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ABSTRACTS

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ORAL SESSION 1. The Role of Electrophysiology in Defining Genotype–Phenotype Correlations of Retinal Dystrophies

Oral paper 1. Keynote Lecture: Support for science and technology in India today

Introduction of Speaker: Dr. Balasubramaniam
Keynote Speaker: Dr. T. Ramasami, Secretary, Department of Science and Technology, Government of India

Oral paper 2. Recent advances in genetics of retinal dystrophies

Chitra Kannabiran
Kallam Anji Reddy Molecular Genetics Laboratory, LV Prasad Eye Institute, Hyderabad, India

Molecular genetic advances have resulted in the identification of new genes for retinal dystrophies, and knowledge of the functions of these genes in the retina. The challenge of genetic screening and its translation to clinical settings lies in the high degree of genetic heterogeneity with about 40 loci known for retinitis pigmentosa alone. This degree of heterogeneity makes it expensive and time-consuming to carry out genetic testing. An accurate classification of patients on the basis of phenotypes can be used to guide and prioritize screening so that genes that are more likely to be involved for a given phenotype can be screened preferentially. Newer high throughput methods based on microarray have enabled screening of several genes at once and if cost-effective, may be a rapid alternative to conventional methods. Genetic testing of patients not only helps in understanding the basis of disease, but also generates data that can be used to select and recruit subsets of patients who may be suitable for specific therapies. Therapeutic approaches that circumvent the genetic heterogeneity of retinitis pigmentosa and related disorders are being developed that rely on regeneration or preservation of photoreceptors based on supplements of vitamins, antioxidants, growth factors, etc. In addition, gene-based therapies such as that of the RPE65 gene in LCA have shown promise and are being tested in clinical trials.

Oral paper 3. Retinal morphology in patients with X-linked retinoschisis evaluated by Fourier Domain Optical Coherence Tomography

Christina Gerth[1], Robert J. Zawadzki[2], John S. Werner[2], Elise Heon[1]
[1]Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children and University of Toronto, Toronto, Canada; [2]Department of Ophthalmology & Vision Science, Vision Science and Advanced Retinal Imaging Laboratory, University of California, Davis, USA

Purpose: (1) To investigate retinal structure and lamination in patients affected with X-linked retinoschisis (XLRS). (2) To correlate retinal morphology with visual function and genotype. *Methods*: Patients with XLRS and an identified genotype were assessed. Vision function tests included visual acuity (VA), color vision and cone and rod mediated function elicited by ISCEV standard and rod-mediated bright flash electroretinogram (ERG). A high-resolution Fourier domain optical coherence tomography (Fd-OCT) system (axial resolution; 4.5 μm, acquisition speeds: 10,000 A-scans/frame, 9 frames/second) constructed at the UC Davis Medical Center combined with a hand-held scanner (Bioptigen

Inc) was used for retinal imaging. Macular images were evaluated with respect to schisis presence/localization and retinal layer integrity. *Results*: Six patients aged 12.6–38.7 years with XLRS and identified mutations in XLRS1 were tested. VA ranged from 0.2 to 1.6 log MAR. ERG responses showed an electro-negative waveform and reduced cone-mediated function in all patients. Rod photoreceptor function was abnormal in one patient. Fd-OCT images revealed foveal schisis involving the outer nuclear layer in 4/6 patients. Extrafoveal schisis within the outer nuclear, inner nuclear and ganglion cell layer alone or in combination was observed in 6/6 patients. The photoreceptor outer and inner segment layers were disrupted and irregular in all patients. Bullous foveal schisis was associated with younger age. No correlation between retinal layer abnormalities and visual acuity, color vision or genotype was found. *Conclusion*: Retinal dystrophy in XLRS is reflected by morphological changes within the inner and outer retinal layers and disrupted photoreceptor integrity. Retinal layer abnormalities are correlated with age but not with visual function nor the genotypic variation.

Oral paper 4. Effects of prolonged dark adaptation in patients with retinitis pigmentosa of Bothnia type: an electrophysiological study

Marie S. I. Burstedt, Ola Sandgren, Irina Golovleva, Lillemor Wachtmeister
Department of Clinical Sciences/Ophthalmology, Umeå University, Umea, Sweden

Purpose: To describe the phenotype Bothnia Dystrophy (BD) with a high prevalence (1:3,600) in Verbotten County, Sweden. This phenotype of recessive retinitis punctata albescens (RPA) with retinal degeneration and maculopathy is caused by a missense mutation R233W in the cellular retinaldehyde-binding protein (CRALBP), localized in the RPE and Muller cells of the retina causing an extremely prolonged dark adaptation (DA) in the BD disease. *Methods*: Ophthalmologic examination and full-field electroretinography (ERGs) after 24 h of dark adaptation were performed and compared in young BD patients. *Results*: The phenotype of BD is described and after extremely prolonged DA (24 h) followed by ERGs. The rod b-wave and the mixed rod-cone a-wave responses reached normal but delayed amplitudes in the ERGs. The oscillatory response increased to the normal level. There was no recovery of the cone response. *Conclusion*: The unique phenotype of BD is presented; during extremely prolonged DA, there is a significant and additional capacity of recovery of the rod function and also a significant increase in activity in the inner retinal layer. A continuous but slow regeneration of rod photopigment seems to occur at least up to 24 h. The visual process in the RPE is retarded and CRALBP acts in this process and the Muller cells of the retina also seem to be involved. The findings support an extremely slow synthesis of photopigments and an irreversibly disturbed cone function early in BD.

Oral paper 5. Genotypic and phenotypic correlation of Bietti's crystalline dystrophy in Chinese patients with CYP4V2 mutation

Timothy Y. Y. Lai, Michael T. K. Ng, Jasmine W. S. Ngai, Pansy O. S. Tam, Dennis S. C. Lam, Chi-Pui Pang
The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, PR China

Purpose: To evaluate the genotypic and phenotypic correlations of Bietti's crystalline dystrophy (BCD) in Chinese patients with CYP4V2 gene by mutation screening and visual electrophysiology. *Methods*: A cross-sectional study of 18 patients in 13 families with BCD was conducted. Patients underwent ophthalmic examination, EOG, full-field ERG, and mfERG examinations. Genomic DNA was extracted from peripheral blood leukocytes and the exons containing the open reading frame of the CYP4V2 gene and the flanking intron splice sites were individually amplified by PCR and sequenced. *Results*: All BCD patients were confirmed to have mutations in the CYP4V2 gene. Nine different mutations in the CYP4V2 gene were identified including five novel mutations. The commonest mutation was the IVS6 to 8del17bp/insGC mutation, followed by the IVS8-2 A $\rightarrow$ G mutation. The mean EOG Arden Index was 1.4 (range 1.1–1.8). Patients with splice site mutations, i.e. homozygous IVS6 to 8del17bp/insGC mutations or with compound heterozygous IVS6 to 8del17bp/insGC and IVS8-2 A $\rightarrow$ G mutations had lower EOG Arden index ($P = 0.014$), and were more likely to have non-recordable scotopic full-field ERG ($P = 0.003$) and non-recordable 30 Hz flicker ERG ($P = 0.043$). *Conclusions*: BCD patients with homozygous IVS6 to 8del17bp/insGC mutation or with compound heterozygous IVS6 to 8del17bp/insGC and IVS8-2 A $\rightarrow$ G mutations appeared to have more severe diseased phenotype based on electrophysiology.

Oral paper 6. A previously undescribed autosomal recessive retinal dystrophy

G. E. Holder[1,2], R. Burgess[3], I. D. Millar[3], B. P. Leroy[4], J. E. Urquhart[3], I. M. Fearon[3], E. De Baere[4], P. D. Brown[3], A. G. Robson[1,2], G. A. Wright[1], P. Kestelyn[4], A. R. Webster[1,2], F. D. C. Manson[3], G. C. Black[3]

[1]Moorfields Eye Hospital, London, UK; [2]Institute of Ophthalmology, London, UK; [3]Academic Departments of Ophthalmology and Medical Genetics, Manchester, UK; [4]Departments of Ophthalmology and Medical Genetics, Gent, Belgium

Purpose: To describe a novel autosomal recessive retinal disorder. *Methods*: Seven patients from five families in two countries were ascertained with progressive visual loss and punctate retinal flecks. All patients received full ophthalmic examination, ERGs, PERG, EOG and fundus autofluorescence imaging, and gave DNA for mutational screening. They had previously received a variety of diagnoses, including ''Goldmann-Favre syndrome'', ''fundus flavimaculatus'' and ''unrecognised dystrophy''. *Results*: All patients had reduced visual acuity, were hyperopic and had irregularity of the RPE reflex with widespread subretinal deposits. A maculopathy was associated with intra-retinal or subretinal fluid in four cases. Autofluorescence imaging was particularly useful in demonstrating these signs. Angle-closure glaucoma was present in two cases. All patients had abnormality of both rod and cone full-field ERG responses, with a delay in the cone flicker ERG. All had abnormal EOG light-rise. Progression in ERG abnormality was documented in three families. Genetic analysis was performed. *Conclusion*: A novel retinal disorder is described. The distinctive clinical and electrophysiological features enable directed mutational screening the results of which will be discussed.

ORAL SESSION 2. Electrophysiological Assessment in Human Retinal Diseases

Oral paper 7. Role of the foveal pit: electrophysiology and functional anatomy of foveal hypoplasia

Michael F. Marmor[1], Stacey S. Choi[2], Robert J. Zawadzki[2], John S. Werner[2]
[1]Stanford University, CA, USA; [2]University of California, Davis, CA, USA

Purpose: To relate visual acuity and the absence of a foveal pit to the structure and function of foveal cones. In albino subjects, with relatively good visual acuity and no nystagmus, we obtained multifocal ERGs (mfERG) and images of central cones with adaptive optics (AO). *Methods*: Four subjects with presumed partial oculocutaneous albinism were studied. VERIS mfERG recordings were made according to ISCEV guidelines, using a matrix of 103 pixels. Two AO imaging systems, AO-flood illumination and AO-high resolution Fourier domain OCT, were used to acquire images of cone photoreceptors and retinal layers from one subject with 20/25 visual acuity. *Results*: Visual acuity ranged from 20/25 to 20/50. OCT images showed no foveal depression, except for one subject with a very weak pit (acuity 20/50). The mfERG responses were normal in all, including the central foveal pixel. However, analysis of signal density ring ratios suggests a possible mild weakness of foveal signal relative to surrounding areas in the afoveate subjects. All subjects showed prominent lengthening of foveal cones, and the central cone images showed relatively normal cone diameter at 1–2° of eccentricity, with only mild disorganization. *Conclusions*: This study poses a dilemma: How can acuity be quite good without a foveal pit? The absence of a pit traditionally signifies poor vision, and poor visual acuity from macular dysfunction is typically associated with reduced mfERG. However, our data indicate that a pit is not required for relatively normal foveal cone anatomic specialization and electrical responsiveness. The critical factors for visual acuity may be neither the anatomic pit nor cone numbers alone, but the degree to which direct cone-to-bipolar transmission is preserved in order to allow resolution and produce a local ERG response.

Oral paper 8. Electrophysiological findings in Bietti's crystalline dystrophy

Bijoy K. Nair, Priya R. Reddy, Divya N. Nair, Kiran K. Daswani, Parveen Sen
Medical Research Foundation, Sankara Nethralaya, Chennai, India

Purpose: To investigate the electrophysiological findings in Bietti's crystalline dystrophy. *Methods*: Four eyes of two subjects (mean age 35.55 years) clinically diagnosed as Bietti's crystalline dystrophy and twelve eyes of six age-matched normals (mean age 35.55 years) underwent Full-field electroretinogram and multifocal electroretinography (mfERG) in accordance with the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV). The patients also underwent visual field testing. One patient underwent EOG. The mfERG stimulus array consisted of 103 hexagons (subtending approximately 44 s of arc horizontally and 36 s of arc vertically at the viewing distance of 40 cm) flickering according to a pseudorandom m-sequence. The first-order kernel response densities were used to calculate the amplitude and implicit times of N1 and P1 responses. *Results*: Multifocal ERGs of the Bietti's Dystrophy patients were compared with those of age-matched normals. Responses were analysed for six concentric rings. The N1 and P1 amplitudes of all

the six rings showed significant difference between normals and patients ($P < 0.05$). The differences in the N1 implicit times of all six rings were not significant ($P > 0.05$). The P1 implicit times of ring 1, ring 3 and ring 4 had significant differences ($P > 0.05$). The full field ERG amplitudes for the single flash rod response, combined response b-wave, single flash cone a-wave and b-wave, and the 30 Hz flicker showed significant differences ($P < 0.05$). The implicit time of scotopic and photopic responses had no significant difference ($P > 0.05$). The combined response a-wave amplitude was not significantly different ($P > 0.05$). EOG done in one subject showed normal Arden ratio (OD-2.322, OS-1.952). *Conclusion*: In Bietti's Crystalline Dystrophy a significant reduction is seen in amplitude of both mfERG and full field ERGs. Multifocal ERG shows significant damage in the mid-peripheral area. The electrophysiological testing in Bietti's Crystalline Dystrophy can provide insight of the functional retina.

Oral paper 9. Acute zonal occult outer retinopathy with central scotoma

Kazuki Kuniyoshi, Akira Nakao, Yoshikazu Shimomura, Yuzo Nakao
Department of Ophthalmology, Kinki University School of Medicine, Osaka, Japan

Purpose: To present the clinical and investigational findings in patients of acute zonal occult outer retinopathy having central or para-central scotoma (central type of AZOOR). *Subjects and methods*: The participants included four males and two females (age range, 21–42 years; mean, 27.5 years) with symptoms of sudden-onset unilateral central or para-central scotoma in the visual field. Funduscopy, fluorescein angiography (FA), colour vision test, perimetry, multifocal electroretinogram (mfERG), full field ERG, optical coherence tomography (OCT), and magnetic resonance imaging (MRI) of the optic nerve and the brain were performed. *Results*: All patients had mild or moderate myopia. During the clinical course, the patient's worst visual acuities ranged from 0.04 to 1.2 and only one patient showed improvement in the final vision. All patients had normal results of funduscopy and FA, and one was found with abnormality in the colour vision test. Perimetry confirmed either central or para-central scotoma in five patients and mf-ERG indicated reduced response density in the macular area in three patients. OCT revealed mild retinal detachment in the macular area in one patient while the other patients had normal MRI results of the optic nerve and brain. *Conclusion*: We consider that sudden-onset unilateral central or para-central scotoma is a feature of the central type of AZOOR. Furthermore, the clinical findings by perimetry, mfERG, and MRI of the optic nerve and the brain are essential to the diagnosis of this disease. However, the prognosis of the central type of AZOOR seemed to be poor.

Oral paper 10. The multi-focal VEP (mfVEP) is able to distinguish between subjects with normal vision and those with wet or dry age-related macular degeneration (AMD)

Suzanne M. Petratchkov[1], Yanti Rosli[2], Andrew James[1], Ted L. Maddess[1]
[1]ARC Centre for Excellence in Vision Sciences, Centre for Visual Science, The Research School of Biological Sciences, The Australian National University, Canberra, Australia; [2]Faculty of Allied Health, UKN, Kuala Lumpur, Malaysia

Purpose: To examine the utility of the mfVEP in the diagnosis of AMD. *Methods*: VEPs to dichoptically presented multifocal stimuli were recorded from normal subjects (aged 50–80 years, 13 male, 10 female), and those with AMD (aged 62–90 years, 8 male, 10 female). The stimulus layout, which subtended the central 23° of the visual field, was an 84 region cortically scaled dartboard comprising 12 sectors and 7 concentric rings. The stimulus presented in each region was a 4 by 4 checkerboard with the black and white checks having a luminance of 0 and 180 cd/m^2, respectively. The individual regions were pulsed on for 33 ms with the mean frequency of pulse presentation being 2 pulses/s/region/eye. Between pulses, the monitor was held at the background luminance of 90 cd/m^2. Responses to each 241.75 s stimulus epoch, which was divided into approximately 30 s or 60 s segments, were recorded using a 64 electrode array in a 10/20 layout. Signal RMS strength of the waveforms over all regions and for the 13 occipital channels only were extracted and subjected to multiple regression analysis where effects for age, gender, sectors, rings and types of AMD were estimated. receiver operator curves (ROC) were constructed to estimate the capacity of this method to distinguish between normal and diseased eyes. *Results*: The multiple regression model accounted for 90% of the variance with F (75,6645) = 830.2, $R^2 = 0.9024$, $P < 0.0001$. Eccentricity was a major factor in being able to distinguish between normal and diseased eyes. For eyes with either dry or wet AMD, the responses in the inner three rings were significantly different ($P < 0.0003$, wet and dry) from those recorded from normal eyes. These responses represent those from the macula alone and

ROCs constructed from these indicated that the discrimination between dry AMD and normal eyes, and wet AMD and normal eyes, was reasonable with areas under the ROC plots being 0.925 and 0.863, respectively. In the case of the apparently normal fellow eyes of the AMD patients, however, only the innermost ring showed a response that was significantly different from that of the normal eyes ($P = 0.015$), with the area under the ROC plot being 0.714. *Conclusion*: mfVEPs show great promise in being able to distinguish between normal eyes and those with a definite diagnosis of wet and dry AMD when responses to stimuli presented to the macula are taken into consideration.

Oral paper 11. Clinical and electrophysiologic criteria for phenotyping retinitis pigmentosa: agreement between two observers

Raja Narayanan[1], Subhadra Jalali[1], Hardeep Pal Singh[2], Anjli Hussain[1], Chitra Kannabiran[2]
[1]Smt. Kanuri Santhamma Centre for Vitreo Retinal Diseases, L V Prasad Eye Institute, Hyderabad, India; [2]Kallam Anji Reddy Molecular Genetics Centre, L V Prasad Eye Institute, Hyderabad, India

Purpose: To establish by inter-observer agreement the relative importance of various signs, symptoms, visual fields and ERG criteria for phenotyping of retinitis pigmentosa. *Methods*: Two masked observers assessed various pre-specified signs and symptoms and investigations done in a cohort of patients diagnosed to have retinitis pigmentosa. Statistical analysis was done to find the agreement between the two observers for each criterion and also for a group of major specified criteria. Criteria studied included nyctalopia, vitreo-retinal changes, ERG changes, visual fields, family history and disease progression. *Results*: Observed agreement between the two observers ranged from 78% to 95% for various criteria. The Kappa value was 0.4–0.6 (moderate agreement) for RPE macular changes, arterial narrowing and progressive visual loss. *Conclusion*: A group of major and minor clinical criteria can be used to establish phenotype for retinitis pigmentosa.

Oral paper 12. Relationship between macular morphology and focal macular electroretinogram in patients with retinitis pigmentosa

Mineo Kondo, Tagasu Sugita, Yoshiharu Nakamura, Chang-Hua Piao, Hirako Terasaki
Nagoya University Graduate School of Medicine, Aichi, Japan

Purpose: To determine whether a significant correlation exists between the macular morphology (macular volume and length of IS/OS line) measured by optical coherence tomography (OCT) and the amplitude of focal macular electroretinograms (fm ERGs) in patients with retinitis pigmentosa (RP). *Methods*: Forty-three eyes of 43 patients with retinitis pigmentosa, who had visual acuity of 0.3 or better, were studied. Fm ERGs were elicited by a 15° spot centred on the fovea under direct fundus observation using a modified infrared fundus camera. The volume in a 6-mm diameter macular area was measured by Stratus OCT (Carl Zeiss). The length of the photoreceptor inner segment/outer segment line (IS/OS line) in a 6-mm diameter macular area was determined from the OCT images. The fm ERG and OCT were also recorded from 20 age-similar normal controls. *Results*: The amplitudes of the a- and b-waves were significantly smaller in RP patients than those in controls ($P < 0.001$). The macular volumes in RP patients were also significantly smaller than those in controls ($P < 0.001$). There was a significant correlation between the macular volume and the fm ERG amplitude (Spearman's rank correlation; $P < 0.01$; $r = 0.44$ for the a-wave; $r = 0.51$ for the b-wave). The fm ERG amplitudes for RP patients with IS/OS line > 2 mm were significantly larger than those for RP patients with IS/OS line < 2 mm. *Conclusions*: Macular morphology (macular volume and length of IS/OS line) measured by Stratus OCT was found to be correlated with the amplitude of fm ERGs in RP patents.

ORAL SESSION 3. Foundations of Visual Electrophysiology: Human and Animal Models

Oral paper 13. Progressive changes in the photopic negative response of the cat ERG following retrograde degeneration of retinal ganglion cells

Suresh Viswanathan, J. Arthur Weber, E. Victor Malinovasky, D. Christine Harman
School of Optometry, Indiana University, Bloomington, USA

Purpose: The purpose of the present study was to determine whether the photopic negative response (PhNR) can detect progressive changes in retinal ganglion cell (RGC) function in a cat model of retrograde degeneration secondary to severe optic nerve (ON) crush. *Methods*: Full-field ERGs were recorded from 11 anesthetized adult cats over 8 weeks following severe unilateral ON crush. Stimuli consisted of 750 ms red flashes delivered on a constant rod-saturating blue

background. Optical coherence tomography (OCT) measurements were performed to document progressive changes in retinal nerve fibre layer thickness (RNFLthk). Animals were sacrificed at 8 weeks and RGC counts were made from retinal whole mounts. The PhNR luminance response function was fitted with a four parameter logistic equation and the change in the estimated parameters of maximum and minimum amplitudes (V_{max} and V_{min}), semi-saturation constant (S50) and slope were studied as a function of time. *Results*: ERG from control eyes showed PhNRs after light onset and offset. Their amplitudes increased with test flash luminance. The coefficients of variation (CVs) of intra- and inter-subject variability were 6% and 24%. The mean average RNFLthk was 41 μm and the CVs for intra- and inter-subject variability of the RNFLthick were 4% and 5%. PhNR to lower luminance levels were almost eliminated in the experimental eyes at 1 week following ON crush. Responses were less severely reduced (by 22%) at higher luminances and progressively diminished over the next 7 weeks. Retinal histology at 8 weeks demonstrated complete loss of RGCs in the sample areas, but thickness of the outer retinal layers appeared normal. Vmax and RNFLthk reduced and S50 constant increased as a function of time. The rate of exponential decay of Vmax and RNFLthk was very similar (~0.03) indicating that their changes over time are closely related. *Conclusions*: In addition to providing further confirmation that the PhNR originates from RGC activity, these results also indicate that the PhNR could hold potential as an objective test for monitoring progressive changes of RGC function.

Oral paper 14. The photopic negative response of the flash ERG to broadband and monochromatic stimuli

Maja Sustar[1], Cvenkel Barbara[2], Jelka Brecelj[1]
[1]Unit for Visual Electrophysiology, Eye Clinic, University Medical Centre, Ljubljana, Slovenia; [2]Department of Glaucoma, Eye Clinic, University Medical Centre, Ljubljana, Slovenia

Purpose: Photopic negative response (PhNR) is negative ERG component that follows the b-wave and was shown to be reduced in diseases affecting retinal ganglion cells, for example in glaucoma. The aim was to investigate the effect of monochromatic and broadband stimuli on the amplitude of the PhNR and to study their sensitivity for detecting glaucomatous damage. *Methods*: Photopic ERGs were recorded from 20 control subjects. Responses were elicited with monochromatic red (635 nm), orange (594 nm), green (513 nm) and broadband white ganzfeld stimuli of progressively higher luminance levels from 0.08 to 7.5 cd s/m^2 in the presence of 10 cd/m^2 blue (470 nm) background. Nine glaucoma patients with moderate to severe visual field defects were included and photopic ERGs (to monochromatic red and broadband stimulus) and pattern ERG were recorded. The group of glaucoma patients will be extended. *Results*: In control subjects the PhNR amplitude was significantly higher ($P < 0.01$) when red monochromatic stimulus was used (25.4 ± 7.1 μV) and it gradually decreased with orange (20.7 ± 6.7 μV) and green (19.3 ± 6.1 μV) monochromatic stimuli, as well as with broadband stimulus of the same luminance (20.3 ± 5.7 μV). This wavelength-dependent pattern of changes was not observed for other ERG components (a- and b-wave). In glaucoma patients the PhNR to red monochromatic stimulus was significantly reduced ($P < 0.001$) and correlated significantly with visual field defects ($P < 0.01$), while significance was not observed for the PhNR to broadband stimulus ($P > 0.05$). The PhNR to a red monochromatic stimulus appeared to be a more sensitive test, with larger area enclosed by receiver-operating characteristic curve (0.97) than the PhNR to broadband stimulus (0.76). *Conclusion*: The PhNR to a red monochromatic stimulus was larger in control subjects and more significantly affected in glaucoma patients than the PhNR to broadband stimulus. These findings suggest that monochromatic red stimulus might be more efficient in eliciting the ganglion cell response than the broadband stimulus.

Oral paper 15. Light-independent ERG-like responses resembling acoustically evoked potentials in mice

Naoyuki Tanimoto[1], Peter Humphries[2], Martin Biel[3], W. Mathias Seeliger[1]
[1]Ocular Neurodegeneration Research Group, Centre for Ophthalmology, Institute for Ophthalmic Research, Tuebingen, Germany; [2]Ocular Genetics Unit, Department of Genetics, Trinity College, Dublin, Ireland; [3]Institute of Pharmacology, Center for Drug Research, Ludwig-Maximilians University, Munich, Germany

Purpose: Electroretinography (ERG) allows us to assess retinal dysfunction in disease as well as the extent of recovery following a therapeutic intervention. In cases when the electrical activity of the retina is reduced, light-independent but event-related responses may dominate the recordings. Following an initial suspicion in mice devoid of both rod and cone function, we examine here the impact of ERG-like acoustically evoked potentials triggered by the sound associated with the generation of flash stimuli in a Ganzfeld system. *Methods*: For this

work, functionally normal wild-type mice (C57Bl/6), mice lacking any retinal function (Cnga3(–/–) Rho(–/–); Claes et al., IOVS 2004), and mice with no auditory function, were examined with Ganzfeld ERG (Multiliner Vision, VIASYS, Germany). Pure auditory responses were generated by a complete blockage of the light stimulus. *Results*: In mice lacking both rod and cone function, small intensity-independent signals were recordable, featuring an initial, a-wave like deflection at about 20 ms, and a subsequent b-wave like deflection peaking at about 40 ms after the flash. In C57Bl/6 wt mice, the same small biphasic responses could be recorded when the flash was blocked, even at flash luminance levels usually too low to produce a discernible ERG waveform. No response was detected under same conditions in deaf mice. The latencies of the two peaks found and the waveform shape correlated well to that of auditory-evoked potentials (Connolly et al., Brain Res 2003). *Conclusions*: In this study, we were able to identify acoustically evoked potentials as a major source of event-related signals in mice of non-visual origin. This finding may be of particular importance for the analysis and interpretation of ERG responses in mice with low light-evoked signal amplitudes.

Oral paper 16. Electrophysiological changes of retinal ganglion cells in RCS rats during retinal degeneration

Zheng Qin Yin, Zhong Shan Chen
Southwest Eye Hospital/Southwest Hospital,
Third Military Medical University, Chongqing, China

Purpose: To study the variations of F-ERG and electrophysiological properties of retinal ganglion cells of RCS rats during retinal degeneration, and to explore the influence of entire retinal function impairment on inner retinal neurons. *Methods*: Two kinds of animal models were used: RCS-rdy + p + rat (black hooded, pigmental eyes, non-dystrophic) as Controls and RCS-p + rat (black hooded, pigmental eyes, dystrophic) as the Test group. The animals were divided into 10 groups, P3W-P12W, according to postnatal age. F-ERG were applied to normal and retinal dystrophic RCS rats. Retinal slices were prepared from rats and patch clamp whole-cell recording was applied to RGCs from birth to postnatal 12th week (P12W). Action potentials were evoked by depolarizing currents in the retinal ganglion cells. The voltage-activated sodium currents were recorded applying a channel blocker under voltage clamp mode. Amplitude, density of sodium currents and *I–V* curves were analysed at different postnatal stages. *Results*: 1. With progressive retinal degeneration in RCS rats, the amplitude of a- and b-wave of F-ERG decreased gradually from P5W, and the waveform appeared silent pattern after P7~8W. 2. Three different discharge patterns of RGCs in response to maintained depolarizing currents were recorded, which were single firing, transient firing and sustained firing. The proportion of each firing type changed significantly during postnatal development. There were no significant differences in the proportion of three AP types between RCS, normal and control rats within 6 weeks of age. At 7–8 weeks postnatal age the proportions of transient firing and sustained firing in RCS rats decreased significantly. At the same time, RGCs with no AP appeared frequently (62.2%). 3. There were no significant differences in current amplitude and density of RGCs sodium channel currents between retinal dystrophic rats ($N = 22$ RGCs) and normal RCS rats ($N = 16$ RGCs) at P21d. However, at the late stage of retinal degeneration action potentials could be evoked in some RGCs (12/18) of retinal dystrophic RCS rats at P60d, and the amplitude and density of sodium currents decreased dramatically. Some sodium currents were still displayed in RGCs without firing. *Conclusion*: 1. Retinal function was impaired in RCS rats with progressive retinal degeneration, which ultimately deteriorates the firing function of RGCs, and influences the projection of visual information from retina to higher centre targets. 2. Action potentials could not be evoked in a proportion of RGCs and the kinetic characteristic of sodium channel changed dramatically at late stage of retinal degeneration. Sodium currents amplitude and density decreased significantly and the *I–V* curve changed, suggesting that the voltage-dependent sodium channel protein of RGCs degenerated at late stage of retinal degeneration. 3. However, some RGCs maintained normal firing function and unimpaired sodium channel current, indicating the possibility of treatment for these diseases.

Oral paper 17. Optimising the detection of transient evoked potentials using a bootstrap re-sampling technique to provide an objective measure of signal recovery

Anthony C. Fisher[1], David M. Simpson[2], Richard P. Hagan[1], Malcolm C. Brown[1]
[1]Clinical Engineering, Royal Liverpool University Hospital, Liverpool, UK; [2]Institute of Sound & Vibration Research, University Southampton; Great Britain, UK

Introduction: Most commonly, the estimation of transient evoked potentials such as the ERG, PERG and VEP is by simple ensemble averaging, synchronized by the stimulation signal. This requires three

assumptions: (i) the signal to be recovered is stationary; (ii) the noise (or 'incoherent' signal component) is stationary with zero mean; (iii) the number of epochs sampled is sufficient to statistically represent the signal of interest within acceptable confidence limits. Whilst ensemble averaging still forms the cornerstone of transient evoked potential measurement, it does not exploit modern statistical signal processing techniques and the potential for extracting more statistical information from the recorded signals. *Purpose*: To describe a statistical bootstrap method that provides an estimate of the probability that the response obtained is due to random variation in the data rather than a physiological response (viz., the null hypothesis). This method can be applied to (almost) any signal parameter (e.g., power, amplitude range, estimates of signal-to-noise ratio) and is based on randomly re-sampling (with replacement) of the continuously recorded data. *Method*: The proposed method was developed and tested initially on simulated data with realistic autoregressive moving average (ARMA) noise. This was extended to a series of clinical PERG recordings. *Results*: The bootstrap model was able to detect the presence of PERG responses at user-defined significance levels in both artificial and clinical recordings. *Conclusion*: The bootstrap re-sampling technique is simple to implement, very flexible in terms of the signal features that can be statistically analysed, and provides a novel means of objectively testing signal recovery. It thus holds the potential to optimize the acquisition process, and to determine the shortest recording time required, based on a clearly defined statistical criterion.

Oral paper 18. Objective measurement of macular pigment optical density and spatial distribution using steady-state chromatic VEPs

Anthony G Robson[1], Neil RA Parry[2]
[1]Moorfields Eye Hospital, London, UK; [2]Vision Science Centre, Manchester Royal Eye Hospital, Manchester, UK

Purpose: To specify isoluminance at different retinal eccentricities and determine macular pigment optical density (MPOD) and spatial distribution using the steady-state chromatic VEP. *Methods*: A colour monitor was used to generate Red/Green (R/G) and Blue/Green (B/G) gratings (2 cycles/degree) within two circular stimulus fields (radius 0.45° or 1.1°) and four annular fields (maximum mean radius 6°). Isoluminance was determined for each subject and every stimulus using heterochromatic flicker photometry (HFP). About 15 Hz onset-offset VEPs were recorded to the same stimuli, changing the luminance ratio between adjacent chromatic components from 0.25 to 0.85 in 11 automated steps. Fourier analysis was used to specify isoluminance objectively, whereby the amplitude of the first harmonic of the steady state VEP is minimised in the absence of luminance contrast. MPOD was computed at each retinal location relative to the most eccentric annulus. To compensate for the broadband phosphor emissions of the monitor, a correction was derived from HFP measurements made through known concentrations of simulated macular pigment (66% Beta-carotene and 34% Alpha-carotene). *Results*: Comparison of HFP with VEP measures of isoluminance showed a gradient of 1.0 and high positive correlation ($r = 0.91$, $P < 0.005$). Corrected MPOD values computed from R/G VEP estimates of isoluminance showed minimal variation between subjects or retinal locations; MPOD values derived from B/G VEPs increased towards the fovea, varied between subjects (maximum 0.35–0.9) and corresponded closely with HFP (slope = 0.85, $r = 0.96$, $P < 0.005$) and with the independent measures of MPOD. *Conclusions*: The steady-state VEP can be used to determine isoluminance at different retinal eccentricities rapidly and objectively. Macular pigment optical density and spatial distribution vary between subjects and can be measured by steady-state VEPs to B/G stimuli.

ORAL SESSION 4. Symposium. ERG in Drug Development: Translation from Animal Models to Human: Part I

Oral paper 19. Overview: the use of the ERG in pre-clinical and clinical drug development

Mitchell G. Brigell
Pfizer Global Research and Development, Michigan, USA

Visual electrophysiological measures can provide early signs of efficacy for new treatments of retinal disease. This information can be used to increase confidence that the drug will have clinically significant benefit on visual function in longer clinical trials. The ERG can also be used as an early indicator of retinal toxicity and can be used to insure patient safety in clinical trials if a pre-clinical retinal toxicity was observed of unknown relevance to humans. In this talk I will present the animal ERG procedure used at Pfizer and will give an overview of how electrophysiological studies can be used to inform drug development.

Oral paper 20. The advantage of electrophysiological tests for assessing retinal toxicity of drugs in laboratory animals

Ido Perlman
Technion-Israel Institute of Technology, Haifa, Israel

Purpose: Drugs that have been developed or suggested for use in the ophthalmic clinic to treat retinal disorders, need to be first examined for possible toxic effects. Our goal is to evaluate the possible retinal toxicity of these drugs in laboratory animals. *Methods*: Drugs, to be tested for retinal toxicity, are injected intravitrealy into one eye, while the other eye, injected with the same volume of physiological solution (saline), serves as control. Electroretinogram (ERG), visual evoked potentials (VEP) and a variety of morphological techniques are used to assess short-term and long-term effects on the retinal function and retinal structure of laboratory animals. *Results*: Dark- and light-adapted ERG responses are recorded simultaneously from both eyes at different time intervals after administration of the studied drug in different concentrations. Since one eye serves as the experimental eye and the other as its own control, comparison between the two in each experimental session circumvents technical factors such as depth of anesthesia from affecting the results. Effects on the functional integrity of the distal retina are assessed from the maximum response amplitude and the semi-saturation constant that are derived from the response-intensity relationship of each ERG wave. The flash-evoked VEP responses are recorded for binocular and monocular stimulation in order to assess functional damage to the inner retina, specifically to the ganglion cells and nerve fibre layer. A variety of morphological techniques; histology, histochemistry and immunocytochemistry are used to identify structural abnormalities and to correlate these with the functional damage. *Conclusions*: The combination of clinical electrophysiology and morphological assessment of retinal integrity is most useful in assessing potential retinal toxicity of drugs in laboratory animals.

Oral paper 21. Detection of early hydroxychloroquine retinal toxicity using multifocal electroretinography ring-ratios

Jonathan S. Lyons[1], Mathew L. Severns[2]
[1]Georgetown University/Washington Hospital Center Program in Ophthalmology, Maryland, USA; [2]LKC Technologies, Inc., Gaithersburg, USA

Purpose: To assess the incidence of decreased retinal function associated with high cumulative dosages of hydroxychloroquine (HCQ) using multifocal electroretinography (mfERG). *Methods*: *Setting*. Clinical practice. *Study population*. 62 patients were referred for evaluation of HCQ retinal toxicity. Controls were 67 normal eyes of 67 patients referred for a variety of conditions in the other eye. *Observation procedures*. Visual symptoms, duration of treatment, cumulative HCQ dosage, condition for which the drug was taken, visual acuity, retinal examination, visual fields, and mfERG. *Main outcome measures*. The average mfERG amplitude was calculated for five concentric rings. The age-corrected amplitude of the central hexagon (R1) and the ratios of R1 to each of the other rings (e.g., R1/R2, R1/R3) were assessed. A measurement was considered abnormal if it exceeded the 99% confidence limits of normal. *Results*: The incidence of characteristic mfERG abnormalities in patients with cumulative HCQ dosages greater than 1,250 g was 40.2%, or 3.9 times that found in patients with less than 1,250 g ($P < 0.001$, Chi-square test). Significant abnormalities were seen with cumulative dosages as low as 400 g. The mfERG abnormality most commonly detected was an increased R1/R2 ratio. *Conclusions*: Functional testing of the retina with mfERG shows a high incidence of locally decreased retinal function in patients who have taken HCQ for extended periods. Although clinical signs or symptoms often accompany the mfERG changes, the clinical findings are often inconclusive. A prudent mfERG testing strategy consists of baseline measurement, retesting at 400 g cumulative dose, then biennial testing until 1,000 g is reached, with annual testing thereafter, unless visual symptoms develop.

Oral paper 22. Treatment of retinal degeneration—ERG in animal models

Mathias W. Seeliger, Regine E. Bauer, Edda Fahl, Eberhart Zrenner, Naoyuki Tanimoto
University of Tübingen, Tübingen, Germany

Diseases affecting photoreceptors and the outer retina, the bipolar cell layer, and the retinal pigment epithelium (RPE) are commonly summarized as retinal degenerations. Although approximately 1 in 3,000 people is affected by retinitis pigmentosa (the most common form) and allied disorders, no drugs or therapeutics against these diseases are currently available.

Rod and cone photoreceptors are the primary neuronal cell types in the retina that capture light and initiate vision. Both in mice and humans, the majority of the photoreceptors are of the rod type (97%) and mediate vision in dim light, whereas cone photoreceptors (3%) mediate high-resolution and colour vision.

Consequently, the loss of rod vision leads to night blindness, and the loss of cone functionality leads to reduced visual acuity and colour blindness. Whereas the dysfunction or degeneration of cones may be limited to the affected system (e.g. in achromatopsia), the loss of rods triggers a subsequent degeneration of cones resulting in a secondary loss of useful central vision and blindness at later disease stages.

As the visual responses travel in form of electrical impulses across the retina, the functional impairment of photoreceptors (rods and/or cones) and the other neurons involved in the transmission and/or processing of these signals can be diagnosed non-invasively by electroretinography (ERG). This is true in particular for bipolar and to some extent for amacrine cells.

This presentation will focus on examples of therapeutic progress in animal models of retinal degenerations that carry either natural or genetically engineered mutations in the respective disease genes, and the role of electroretinography (ERG) in the assessment of the treatment effects.

Oral paper 23. Animal models of oxidative retinopathies: clinical findings and possible therapeutic avenues

Pierre Lachapelle, Allison L. Dorfman, Sandrine Joly, Ewelina Zimak, Adriana Di Polo, Sylvain Chemtob
Department of Ophthalmology, McGill University/ Montreal Children's Hospital, Montreal, Canada

Purpose: Over the past decade we have developed two animal models of degenerative retinopathies, namely: oxygen-induced retinopathy (OIR) with features reminiscent of human retinopathy of prematurity (ROP) and light-induced retinopathy (LIR) with features reminiscent of retinitis pigmentosa (RP). This presentation summarizes what we have learned of the pathophysiological processes involved and our successes in slowing them down. *Methods*: Newborn Sprague Dawley (SD) and Long-Evans (LE) rats were exposed to hyperoxia (80% O2) or a bright luminous environment (10,000 lux) from birth to the end of the first month of life. OIR treatment included: Trolox-C and NOS inhibitors; LIR treatment included: Ad.BDNF, FGF-2 and CNTF. Severity of retinopathy and outcome of treatment were assessed with the electroretinogram (ERG), the visual Evoked Potential (VEP), retinal histology, retinal flat mounts, western blots and immunohistochemistry. *Results*: OIR begins as a vasculopathy and rapidly progresses towards a severe and irreversible impairment of the retinal structure and function beyond the Outer Plexiform Layer (OPL). The latter does not appear to be the direct result of the initial vasculopathy, but a combination of several factors of which retinal maturation appears to be the most important contributor. The resulting retinopathy is significantly more severe in pigmented animals. Treatment with free radical scavengers partly attenuated the retinal and cortical sequelae. In contrast, LIR has detrimental effects on the retinal structure and function above the OPL and beneficial effects on layers below (mostly INL). This retinopathy is significantly more severe in albino animals, pigmented rats demonstrating what appears to be a beneficial effect (thickening of retina and enhancement of ERG). Neurotrophic factors are effective in slowing down the pathophysiological process triggered, although one cannot rule out the possible contribution of free radicals, an avenue that will be explored shortly. *Conclusion*: Our animal models of OIR and LIR offer the unique experimental opportunity to further our understanding of initially inner and outer retinal disorders and explore new therapeutic avenues in retinal disorders that share several common features with their human analogues namely: ROP and RP respectively.

ORAL SESSION 5. Symposium. ERG in Drug Development: Translation from Animal Models to Human: Part II

Oral paper 24. Translation from animal models to human retinal degenerative ischemic diseases

Anne B. Fulton
Department of Ophthalmology, Children's Hospital and Harvard Medical School, Boston, USA

Visual loss occurs in conditions that perturb the exquisite cross-talk between the neural retina and its vascular supplies, the choroidal and retinal circulations. While retinal degenerative conditions are diseases primarily of the neural retina, it is common knowledge that attenuation of the retinal vasculature is a feature of these diseases. Conditions usually attributed to diseased retinal and/or choroidal circulations, including age-related macular degeneration, retinopathy of prematurity and diabetic retinopathy, also involve the neural retina, both photoreceptor and post-receptor. The use of animal models provides an opportunity for efficient definition of the interplay of the neural and vascular components of these diseases. Thus, animal experiments are critical to identification of targets in the neural and vascular networks for novel treatments of these blinding conditions.

Oral paper 25. AMD treatment and prevention—the role of the ERG

Christina Gerth
The Hospital For Sick Children, Toronto, Canada

Age related macular degeneration (AMD) is affecting an increasing number of people, with an estimate of 2.95 million in the USA by 2020 (The Eye Diseases Prevalence Research Group, Arch Ophthalmol 2004). Possible preventive agents such as vitamins and supplements have been studied and promising advances in developing treatment options for AMD have been made in recent years. What role does electrophysiology play as a sensitive outcome measure?

The most commonly used tests are the full field electroretinogram (ERG) and the multifocal ERG (mfERG). Test results from patients with AMD and reduced vision need special attention in respect to fixation pattern, age-matched control data, and retinal luminance depending on lens properties. Advantages, disadvantages and limitations of the techniques will be reviewed along with a review of published studies.

Oral paper 26. Treatment of glaucoma—ERG in animal models

Laura J. Frishman
College of Optometry, University of Houston, Houston, TX, USA

This overview will explore the advantages and disadvantages of various rodent and primate models for research on the glaucoma and its treatment/prevention. The utility of flash and pattern ERGs in all models, as well as the multifocal ERGs in primate models for monitoring progression of the disease and effectiveness of treatments will be discussed. The presentation will also address the benefits of using non-invasive imaging of retinal structure, such as retinal nerve fibre layer thickness measurements, in combination with electrophysiological measures in studies that monitor efficacy of therapies.

Oral paper 27. The PERG as a tool to assess glaucomatous optic nerve

Michael Bach
University-Augenklinik, Freiburg, Germany

Purpose: To review the efficacy of the pattern electroretinogram (PERG) in glaucoma. *Methods*: An overview of the literature, concentrating on the following issues: (1) Importance of the stimulation parameters, i.e., check size and temporal frequency, (2) relative relevance of the various PERG structures (P50, N95) and steady- state responses, and (3) the relation to visual field defects. *Results*: The PERG is markedly altered in glaucoma. Optical imaging on the retina needs to be optimal. There is little difference in glaucomatous affects on the P50 versus N95. A higher temporal frequency (>10 reversals/s) improves the sensitivity to detect glaucoma compared to transient stimulation, and it is no disadvantage that at these frequencies P50 and N95 cannot be distinguished. The ''PERG-ratio'', namely the ratio between the amplitudes to 0.8° checks and to 16° checks, exploits a check-size specific reduction in early glaucoma and reduces inter-individual variability. Various studies (both PERG and mfPERG) relating the PERG with local field defects found little correlation, suggesting that the PERG signals a ''diffuse'' damage mechanism. Longitudinal studies suggest that the PERG can indicate incipient glaucoma damage before it becomes evident from the visual field. *Conclusions*: The PERG is a demanding electrophysiological technique that can serve as a sensitive biomarker for retinal ganglion cell function. With appropriate paradigms, PERG assists in identifying those patients with elevated IOP in whom glaucomatous optic atrophy is incipient before visual field changes occur. Given this high sensitivity, the PERG should also be considered as a tool to assess treatment regimes.

Oral paper 28. Selecting end-points and ensuring quality in multi-center trials

Eberhart Zrenner
University Eye Hospital, Tübingen, Germany

In recent years, electrophysiological non-invasive testing has increasingly become important in pre-clinical and clinical studies, concerning efficacy and safety as well as identification of the possible origin of drug-induced pharmacological or toxicological effects in the visual system. The design of pre-clinical and clinical studies, especially multi-centre studies requires special consideration, not only concerning retinal function, retinal diseases and retinal circuitry as well as biochemistry, but also selection of the proper electrophysiological ''markers'' for appropriate endpoints on the basis of professional knowledge of the possible actions of particular compounds on visual function. Quality has to be ensured by extended standard operating procedures and case report forms that implement the collection of data that test the quality of procedures and of calibrations. Moreover, presently networks of validated centres are forming (http://www.europeanvisioninstitute.org/ct_SE/)

and internet-based technology is available that makes electrophysiological testing in the eye much more easy in terms of quality, quality control, central reading and monitoring as well as data management.

The principles shall be outlined that may help select proper tests on the basis of their specificity for the function of certain retinal cell subgroups. Practical hints will be given regarding which tests, from the large toolbox of instruments that assess function and morphology of the visual system, shall be used to approach questions of safety and efficacy, based on hypotheses that stem from pre-clinical data where psychophysics of the visual system is not available. Moreover, new developments are pointed out that help to improve the quality of multi-centre studies by proper standard operating procedures and stringent case report forms, based on the development of international standards and recommendations in ophthalmology.

ORAL SESSION 6. Vision and Brain Plasticity

Oral paper 29. The changing brain: how visual and other behavioural experiences influence the brain

Sumantra Chattarji
National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore, India

We tend to think of ourselves as the same person throughout life. But the functional output and structural state of the brain changes quite dramatically over the human lifespan—starting from early development of the nervous system onto the mature brain with its full behavioural repertoires, as well as when it is subjected to disease and traumatic insults. The complex architecture of the adult brain is sculpted from a combination of genetic instructions, cellular interactions, and eventually dynamic interactions the organism has with the world around it. The most comprehensive understanding of these changes in neural circuitry has come largely from decades of studies of the developing visual system in mammals. These studies tell us that the initial steps in the construction of the visual circuitry rely primarily on intrinsic molecular and cellular processes. However, once the basic patterns of brain connections are in place, precise patterns of neuronal activity, driven by visual experience, can further modify the synaptic circuitry of the developing visual system. In early postnatal life, neuronal activity generated by visual inputs to the retina thus provides a mechanism by which the outside world can have a profound influence on the internal state of the brain. These activity-mediated effects on the developing visual system are most pronounced during a temporal window in early postnatal life called critical period. In a series of seminal studies, Hubel and Wiesel demonstrated that depriving an experimental animal of normal visual experience during this critical period of postnatal development irreversibly alters neuronal connections and functions in the visual cortex. These observations, which eventually led to the Nobel Prize, provided the first evidence that the brain translates the effects of early visual experience into permanently altered wiring of the visual cortex. These developmental phenomena in the visual system of experimental animals are reflected in clinical problems in children who have experienced similar deprivation, e.g. caused by ''lazy eye'' or cataracts. A growing body of evidence indicates that the visual system of humans exhibits much the same critical period for visual cortical development and behaviour as experimental animals in laboratory settings. In the first part of my talk I will give an overview of findings from the visual system.

As animals mature, the cellular mechanisms that mediate the highly dynamic modulation of neural connectivity during the critical period of development become less effective. However, recent exciting findings suggest that even in the adult brain synaptic connections can be modified as new skills and memories are acquired and older ones are forgotten. Indeed, some of the same cellular mechanisms used during early visual development are evidently retained and adapted to mediate experience-driven changes in the mature brain. Strikingly, the lessons learned from the developing visual system turn out to be very useful for studying experience-induced plasticity of the adult brain. For example, the same rules that govern plasticity in the developing visual cortex also underlie learning and memory in the adult brain. Therefore, the second part of my talk will describe recent findings from my lab that show how the same molecular and cellular mechanisms mediate the storage of memories created by behavioural experiences.

My laboratory is interested in understanding why memories of emotional events are often very powerful and persistent. Why do war veterans or victims of severe stress continue to have vivid flashbacks of traumatic events from their past, while their cognitive abilities diminish? Stress disorders bring these questions into sharp focus because chronic stress has contrasting effects on different types of memories. Stress impairs memories of facts and events, which depend on synaptic plasticity in a brain structure called the hippocampus. In contrast, stress greatly amplifies emotional memories, which are processed by another structure called the amygdala. But little is known about the neural basis for this contrast. Therefore, we study the effects of stressful

experiences on synapses, cells and microcircuits in the hippocampus and amygdala, by using a combination of behavioural, neuroanatomical, genetic engineering and electrophysiological techniques. Using this strategy, we have identified several novel neural correlates of stress-induced plasticity in the amygdala, which are strikingly different from those observed in the hippocampus. Our findings suggest that prolonged stress leaves its mark by enhancing both the physiological and structural basis of synaptic connectivity in the amygdala, thereby triggering the emotional symptoms observed in stress-related psychiatric disorders.

Oral paper 30. GABAA-IPSCs of layer IV neurons in rat visual cortex after exogenous regulation of TPA on PNNs during termination of critical period of visual plasticity

Sha Zheng, Zheng Qin Yin
Southwest Eye Hospital/Southwest Hospital,
Third Military Medical University, Chongqing, China

Purpose: Aim of this study was to investigate the synaptic transmission mechanisms by which tissue-type plasminogen activator (tPA) may contribute to termination of the critical period of visual plasticity through the GABAergic inhibitory interneurons by disintegrated perineuronal nets (PNNs) which are mainly composed of chondroitin sulphate proteoglycans (CSPG) molecules. *Methods*: The exogenous tPA or its inhibitor tPA-stop dissolved in artificial cerebrospinal fluid (ACSF) were given to infuse and incubate visual cortex slices of rats at postnatal weeks (PW) 3, 5 and 7 respectively, with pure ACSF infusion on visual cortex slices at each week-age as the normal control. Patch-clamp whole-cell recording technique was used to examine the GABAA-IPSCs of layer IV neurons in visual cortex slices infused by normal, tPA and tPA-stop, respectively. Immunohistochemistry was used after the electrophysiological recording to examine the effect of exogenous tPA regulation on PNNs of layer IV neurons in visual cortex at those three different week-ages. *Results*: (1) Exogenous tPA or tPA-stop infusion on visual cortex slices had no influence in number of PNNs-positive neurons, but exogenous tPA infusion degraded PNNs making their appearance disintegrated. (2) The decay time, peak value and IPSCs/PSCs ratio of GABAA-IPSCs were significantly decreased after exogenous tPA infusion. (3) The trending curves of decay time, peak value and IPSCs/PSCs ratio of GABAA-IPSCs were moved posterior after exogenous tPA infusion, and moved forward after exogenous tPA-stop infusion. *Conclusion*: The mechanisms by which tPA contributes to termination of the critical period of rat visual development may be due to its proteolytic activities on PNNs formation, resulting in regulating maturation of GABA inhibitory neural circuits in layer IV of visual cortex. Exogenous tPA infusion inhibits maturation of GABAA mediated inhibitory neurotranmission in layer IV of visual cortex and delays the critical period of plasticity by degrading PNNs. Exogenous tPA-stop infusion can advance the developmental timing of GABAergic inhibitory synaptic function in layer IV of visual cortex.

Oral paper 31. Visual evoked potentials in successfully treated amblyopic children are impaired

Dave Saint-Amour, Judith Hotte-Bernard,
Marie-Lyne, Jean-Louis Jacob, Marie Sylvie Roy
Sainte-Justine Hospital, Centre de recherche,
CHU Sainte-Justine, Montreal, Canada

Purpose: Successful treatment of amblyopia is clinically achieved when the visual acuity reaches a Snellen score of 20/30 or better. Recent studies, however, suggest the presence of abnormal visual processing in successfully treated amblyopic eyes compared to normal. This study aimed to assess the functional integrity of the visual cortex with electrophysiological measures after a successful clinical treatment of amblyopia by patching. *Methods*: Eighteen successfully treated amblyopic children and 19 normal children were tested. The age range was 6–12 years. Pattern-reversal visual evoked potentials (VEPs) were recorded at Oz in response to stimuli defined by two standard spatial frequencies (0.5 and 2.5 cycles/degree) and four contrast levels (4%, 12%, 28% and 95%). Statistical differences were assessed using three-way (Group × Frequency × Contrast) repeated measures ANOVA. *Results*: An interaction Group × Contrast was observed for the N75 latency. Indeed, the N75 was significantly delayed in the treated amblyopic eyes as compared to the non-amblyopic eyes but this difference appeared at 4% contrast only. No effect for the amplitude of the N75 was found. A main effect of Group was found for the latency of the P100. The P100 was significantly delayed in the treated amblyopic eyes compared to the non-amblyopic eyes. Finally, we found a main effect of Group for the P1 amplitude, such that the P1 amplitude was significantly lower in the treated amblyopic eyes when compared to both the non-amblyopic and the normal eyes. *Conclusion*: This study suggests that a successful clinical treatment does not necessary imply a complete recovery of visual function. Our finding observed at the 4% contrast level suggests a preferential alteration of the magnocellular system. Furthermore, the residual deficit is likely to involve

extra-striate areas because of the origin of P1 generators.

Oral paper 32. Study of P-VEP in high hyperopic anisometropic amblyopia in children after LASIK

Hui Wang, Zheng Qin Yin, Qian Ren
Southwest Eye Hospital/Southwest Hospital, Third Military Medical University, Chongqing, China

Purpose: To assess improvement of P-VEP during amblyopic therapy after laser in situ keratomileusis (LASIK) in high hyperopic anisometropia with amblyopia in paediatric patients. *Methods*: 42 children with high hyperopic anisometropic amblyopia were studied in this prospective, non-comparative and interventional case research. The age of the children ranged from 6 to 14 years. LASIK was performed in the higher hyperopic eyes under topical or general anaesthesia using the SummitU + 00Al¯s SVS Apex plus£L mask for simple hyperopia (9 eyes), P mask for hyperopia and astigmatism: 12eyes£© and the LumenisU + 00Al ¯s Allegretto Wave (21 eyes). Routine amblyopic therapy was performed in all the patients after LASIK. The preoperative and postoperative outcomes of pattern VEP (PVEP) were analysed. Minimum follow-up was 6 months and 24 children had 2-year follow-up. *Results*: Before surgery, the peak latency of the P100 wave of the PVEP was 123.35 (±25.1) ms and the P100 amplitude was 13.66 (±4.78) μv. The latency of P100 was 115.30 (±15.9) ms, 112.73 (±15.5) ms and 109.86 (±9.25) ms, respectively at 6, 12, 24 months postoperatively, which had significant differences compared with preoperative results. The amplitudes of the P100 waves were 16.05 (±5.21) μv, 15.81 (±6.18) μv and 18.44 (±6.07) μv, respectively at 6, 12, 24 months postoperatively, which also had significant differences compared with preoperative values. *Conclusion*: The peak latency of P100 wave of the PVEP was shortened and the P100 amplitude was increased in children with high hyperopic anisometropic amblyopia after LASIK, which implies that the visual function of those patients could be improved by the amblyopia therapy after LASIK.

Oral Session 7. Evolving Role of Visual Evoked Potentials in Neuro-Ophthalmology

Oral paper 33. Overview of the evolving role of visual evoked potentials in neuro-ophthalmology

Colin Barber, Chea Lim, Yaqin Wen
Queen's Medical Centre, Nottingham, UK

For 35 years, ever since Halliday's pioneering work in optic neuritis, the VEP has played a valuable diagnostic role in neuro-ophthalmology. But it has never really moved significantly beyond this core application.

This review will discuss the underlying reasons for this state of affairs, and ask whether the relatively recent development of the multifocal VEP (mVEP) has altered the situation. It will explore the promise and potential of the mfVEP and show, using clinical examples from our own lab and others, why we believe it marks a seminal stage in the evolution of VEPs in neuro-ophthalmology.

Oral paper 34. VEP in diagnosing visual pathway maldevelopment in children

Jelka Brecelj[1], Branka Stirn-Kranjc[2], Nuška Pečarič-Meglič[3]
[1]Unit for Visual Electrophysiology, Eye Clinic, University Medical Center, Ljubljana, Slovenia; [2]Department of Pediatric Ophthalmology, Eye Clinic, University Medical Center, Ljubljana, Slovenia; [3]Clinical Institute of Radiology, University Medical Center, Ljubljana, Slovenia

Purpose: Absent or reduced visual pathway decussation at the chiasm (defined as achiasmia) is associated with distinctive flash VEP asymmetry. Previously, we have demonstrated in two children that ipsilateral N2 wave distribution can define achiasmia. In our cases neuroimaging revealed that absent or reduced chiasmal decussation was associated with hypoplastic optic nerves and tracts and in some cases with other CNS abnormalities. The aim was to study asymmetry of the monocular VEP response to flash and onset stimulation in comparison to age matched controls and children with albinism. *Methods*: Four children with congenital nystagmus, reduced visual acuity and with MRI-confirmed hypoplastic optic nerves, achiasmia and hypoplastic optic tracts (and in two cases with other CNS abnormalities), 17 healthy age matched controls and 5 children with albinism were studied. VEPs to monocular flash and to pattern onset were recorded from three occipital electrodes. *Results*: In children 1 and 2 with hypoplastic optic nerves, achiasmia and hypoplastic tracts (child 2 had other CSN abnormalities) there was asymmetry of the monocular VEP response to flash stimulation distinctive for achiasmia. In children 3 and 4 with hypoplastic optic nerves, achiasmia and hypoplastic right tract (child 3 had other CSN abnormalities) there was asymmetry of the monocular VEP response to flash stimulation in accordance to right tract maldevelopment. VEP asymmetry present in all 4 children to onset stimulation was less distinguishing, while to flash

stimulation was very distinctive when compared to healthy age matched children and to children with albinism, where there is an excess decussation of optic nerve fibres at the chiasm. *Conclusions*: Congenital nystagmus can be associated with abnormalities in the development of the visual pathway, which might be revealed by VEP asymmetry to monocular flash stimulation. VEP asymmetry can indicate the need for further MRI scanning.

Oral paper 35. Pattern and flash VEPs in children with optic pathway glioma

Dorothy A. Thompson[1,2], Arun Dev-Borman[3], Darren Hargrave[4], Samantha M. Hayton[1], Alki Liasis[1], R. Jane Leitch[3]
[1]The Tony Kriss Visual Electrophysiology Unit, Great Ormond Street Hospital for Children, London, UK; [2]Visual Science Unit, Institute of Child Health, University College, London, UK; [3]Eye Dept, Sutton Hospital, Surrey, UK; [4]Paediatric Oncology Unit, Royal Marsden, Sutton, UK

Purpose: We set out to study the range and nature of visual electrophysiological findings in a sample of paediatric patients with optic pathway glioma compared to standard clinical findings so we might address the recent interest in using VEPs to detect optic nerve gliomas and correlate visual field defects in these patients. *Methods*: A retrospective review of the VEP findings of 18 patients identified with low-grade optic pathway gliomas (OPG) who presented to one ophthalmologist (RJL) was carried out. VEPs were recorded to ISCEV paediatric recommendations; three occipital electrodes were referred to a mid-frontal electrode. A range of high contrast black and white checks size were presented (400′–6.25′), in a 28° field. Pattern reversal, pattern onset/offset and flash stimulation was used. Averages were acquired and stored for offline analyses using a 'Diagnosys Espion' system. These data were compared to clinical ophthalmological examination findings that included fundoscopy, VA to age appropriate tests, visual fields and colour vision where possible. *Results*: Only one patient had normal VEPs from one eye. The others demonstrated an array of VEP waveform, amplitude, and latency changes and trans-occipital asymmetries: e.g. a 2.75-year patient showed a homonymous uncrossed trans-occipital VEP distribution a year before it was possible to detect a field defect by confrontation. Although good small check VEPs broadly agreed with good graded visual acuity there were discrepancies where good to moderate behavioural VA was associated with poor VEPs. Such discrepancies arguably have greatest clinical value; e.g. a 2-year-old patient who had achieved age appropriate, normal VA values, and whose parents did not consider there was any visual problem, had very poor VEPs each eye. As a result, treatment was started. *Conclusions*: VEPs are not formally included in assessment protocols for OPG across the world, because of limited availability and cost. Our data emphasise that the VEP can provide a different measure of pathway function to behavioural acuity and fields. It is incomplete to analyse VEP results only as amplitude and latency measures. VEPs can have particular value in paediatric OPG cases when ceiling effects of behavioural tests may disguise the extent of functional involvement.

Oral paper 36. Structural and functional evaluation of retina and optic nerve in patients with multiple sclerosis without optic neuritis attack

Fatih C. Gundogan[1], Şeref Demirkaya[2], Gungor Sobaci[1]
[1]Department of Ophthalmology, Gulhane Military Medical Academy, Ankara, Turkey; [2]Department of Neurology, Gulhane Military Medical Academy, Ankara, Turkey

Aim: To determine: (1) the association of retinal neurodegeneration in MS without optic neuritis attack, (2) the value of structural and functional tests in evaluation of retinal neurodegeneration in multiple sclerosis (MS) patients without clinically-proven optic neuritis. *Methods*: Nineteen patients with a diagnosis of definite MS who had not been affected by optic neuritis attack, and 37 age- and sex-matched control subjects were enrolled. Retinal nerve fibre layer (RNFL) thickness was determined by optical coherence tomography (OCT, Zeiss). The measurements in each quadrant (superior, nasal, inferior, and temporal) were averaged. The data in all quadrants were identified as $RNFL_{overall}$, whereas the data obtained in the temporal quadrant-only were identified as $RNFL_{temporal.}$ Pattern visual evoked potentials (PVEP) was recorded by using high contrast (99%) checkerboard stimuli subtending 15′ and 60′ of the visual arc. Multifocal electroretinogram (mfERG) response to a scaled 61 hexagonal pattern was averaged over five concentric rings (R1-R5). PVEP, ERG, and mfERGs were recorded using Roland Consult RetiSCAN system. Only the right eyes were included in the groups. *Results*: There was a significant ($P = 0.007$) reduction in $RNFL_{temporal}$ thickness in MS patients (study group: 70.2 ± 2.8, control group: 84.6 ± 17.1 μm). P100 latency was significantly prolonged, and P100 amplitude was significantly reduced for both 60′

and 15′ checks ($P < 0.05$). Rod response b wave implicit time, maximum combined response, and a- and b-wave implicit times were significantly prolonged ($P = 0.03$, 0.009, < 0.001, respectively). There was no significant difference in mfERG responses in all concentric ring analysis ($P > 0.05$). $RNFL_{temporal}$ was correlated to P1 peak implicit time in the central ring (R1) in mfERG ($P < 0.05$, $r = –0.598$), P100 latency for both 60′ checks ($P < 0.05$, $r = –0.387$) and for 15′ checks ($P < 0.05$, $r = –0.441$), and P100 amplitude for 15′ check ($P < 0.05$, $r = 0.431$). The most sensitive parameter, P100 latency to 60′ check size, detected 11 of 19 patients (58%) outside limits of the 95th percent confidence interval for normative data. *Conclusion*: Retinal neurodegeneration exists in MS without optic neuritis attack, and PVEP and OCT values obtained from RNFL seems to be sensitive and may be used as a biomarker in MS.

Oral paper 37. Visual electrophysiological markers of drug toxicity in children

Carol A. Westall, Aphrodite Dracopoulos, Fil Cortese, Thomas Wright, Raymond Buncic, Rita Nobile
The Hospital for Sick Children, Toronto, Canada

Purpose: Children with infantile spasms (IS), an age related epilepsy syndrome occurring during infancy, treated with the anti-epileptic drug vigabatrin are risk for retinal toxicity. Our purpose is to determine which markers show change with vigabatrin treatment compared with pre-drug treatment. Vigabatrin attributed toxicity is determined by sustained reduction in 30 Hz flicker response. *Methods*: Prospective, longitudinal study including 130 paediatric patients on vigabatrin therapy (age drug started 1–25 months of age). Informed consent was obtained from the parent/guardians according to the guidelines of the Helsinki declaration. Patients were tested first before vigabatrin therapy. Sequential ERGs were recorded at 3- or 6-month intervals. Longitudinal data were collected on multiple occasions (2–10 visits, mean = 4). About 72 patients were on vigabatrin monotherapy, 60 were female. ERGs were recorded after chloral hydrate sedation according to ISCEV standards. In addition, photoreceptor (cone and rod) responses using a very bright flash (4 log scot td-s), photopic negative response and multifocal ERGs were recorded. Visual evoked potentials were used to determine grating acuity and contrast sensitivity. All data were age-corrected. *Results*: Drug treatment longer than 12 months was associated with increased incidence of toxicity compared with less than 12 months (Chi square $P = 0.016$). In addition to reduction in 30 Hz flicker amplitude after 1-year of treatment, the last photopic OP response (OP4) and cone b-wave amplitudes were reduced and the 30 Hz flicker implicit time delayed. Multifocal ERGs showed change with drug treatment as did the photopic negative response. Contrast sensitivity was reduced before drug treatment and showed no further reduction with treatment. *Conclusion*: The use of electrophysiological markers to determine which visual electrophysiological markers show change with drug treatment will allow in determination of the major site of defect (photoreceptor to ganglion cell) and if ERG defects translate into visual (VEP) defect.

Oral paper 38. Flash and Flicker VEPs in newborn term infants of drug-misusing mothers

D. L. McCulloch[1], L. McGlone[2], M. S. Bradnam[3], M. Hepburn[4], R. Hamilton[3], W. Borland[5], R. Boulton[3], C. Pieh[6], M. Bach[7], H. Mactier[2]
[1]Vision Sciences, Glasgow Caledonian University, Scotland, UK; [2]Neonatal Unit, Princess Royal Maternity Hospital, Scotland, UK; [3]Clinical Physics, Royal Hospital for sick Children and University of Glasgow, Scotland, UK; [4]Obstetrics, Princess Royal Maternity and University of Glasgow, UK; [5]Drug Investigation Unit, Biochemistry Department, Gartnavel General Hospital, Glasgow, UK; [6]Department of Ophthalmology, University of Freiburg, Germany; [7]Universitäts-Augenklinik, Freiburg, Germany

Purpose: Prenatal exposure to drugs of misuse may be associated with delayed visual maturation. We used VEPs to assess the function of the visual system in drug-exposed infants in the first 2 weeks of life. *Methods*: Subjects were 42 term infants who were clinically well; 21 born to drug misusing mothers who had been prescribed methadone during pregnancy and 21 non-exposed infants. VEPs were recorded in the first 4 days of life to a bright flash (25 cd s/m^2) delivered at 1 Hz. and to flicker at six frequencies ranging from 2.9 to 38 Hz (50 cd/m^2, ON/OFF with 50% duty cycle) in 9 drug-exposed and 20 non-exposed infants. Flash VEPs were classified by waveform and reproducibility. Amplitude was measured from the largest peak to trough. For flicker VEPs, magnitude, SNR and *P*-values were evaluated at the stimulus frequency (F1) and at its first harmonic (F2). After 1 week, VEPs were repeated in 14 of the drug-exposed infants, seven of whom required treatment for neonatal abstinence syndrome (NAS). *Results*: All non drug-exposed infants had well-reproduced flash VEPs and significant VEPs to the 4.6 Hz flicker at F1, F2 or both ($P < 0.05$). VEPs were less

reliably detected for all other flicker rates. Infants who were awake had a significant F2 for the 4.6 Hz flicker VEP (8/11) more often than those who were sleeping (5/12). Flash VEPs showed no difference based on sleep state. Urinalysis in the drug-exposed infants, confirmed methadone as well as illicit opiates and/or benzodiazepines in the majority. In these infants, neonatal flash VEPs were markedly smaller in amplitude ($P < 0.001$), fewer showed typical waveforms and five were undetectable ($P < 0.01$). After 1 week, flash VEPs in the drug-exposed infants had improved significantly but remained smaller and poorer in quality than those of the non-exposed infants at birth. The 4.6 Hz flicker VEPs also showed deficits ($P < 0.01$): only 6/9 had significant VEPs at either harmonic, only one of these had a significant F2. *Conclusion*: These data are consistent with clinical experience of delayed visual maturation in infants exposed to drugs in utero. Neonatal VEPs are adversely affected by maternal drug misuse. Further investigation is warranted to identify potential contributing effects of maternal methadone and benzodiazepine use and/or oral morphine used to treat NAS.

POSTER SESSION 1. Group A. Clinical Applications of mfERG

Poster A1. The Role of Electrophysiological Testing in Patients with Acquired Ocular Syphilis

Yaqin Wen[1], Colin Barber[1], Andrew Browning[2]
[1]Department of Medical Physics, Nottingham University Hospitals NHS Trust, UK; [2]Department of Ophthalmology, Nottingham University Hospitals NHS Trust, UK

Purpose: To describe electrophysiological changes in three patients with acquired ocular syphilis both before the diagnosis of systemic syphilis and following treatment with penicillin. *Methods*: Three patients with a provisional diagnosis of acquired ocular syphilis were referred to us for electrophysiological investigations. Initially serial visual electrophysiological recordings, including pattern reversal VEP, standard ERG and multifocal ERG (mfERG) (using VERIS 4.7), were performed on all three patients to assess their retinal and optic nerve function. Treatment for neurosyphilis (penicillin) was initiated after the provisional diagnosis was confirmed, and they were referred back to us to monitor progression. The pattern reversal VEP and mfERG were repeated three or four times over 6 or 12 months following the treatment. Both amplitude (peak to trough) and latency of the P100 component of the pattern VEP were measured for all three patients (five eyes). The first kernel responses of the mfERG were analyzed. The amplitude (peak to trough) and latency of the first positive peak (P1) component of the average responses from four concentric rings were measured for each patient. *Results*: Initially, both the pattern reversal VEP and the mfERG were reduced and delayed in all three patients. The standard ERG was still within the normal limits in some, mildly affected, eyes, but was reduced in other severely affected, eyes. After the treatment, visual acuity improved significantly (from 1/60 to 6/6) and rapidly within the first 3 months post treatment. The mfERG showed an improvement in P1 amplitude of responses from four concentric rings over the monitoring period. However, the P1 latency did not change significantly. *Conclusion*: Syphilitic ocular manifestations do not show any typical characteristics and early diagnosis with adequate treatment is very important in this serious but treatable condition. This preliminary study shows that VEP and ERG, particularly mfERG, are very useful not only in establishing diagnosis, but also in monitoring progression during the recovery period.

Poster A2. Multifocal electroretinography in X-linked retinoschisis

Parveen Sen, Sanjiv Maru, Priya R. Reddy, Bijoy K. Nair, Kiran K. Daswani
Sankara Nethralaya, Medical Research Foundation, Chennai, India

Purpose: To study multifocal electroretinography (mfERG) responses in X-linked retinoschisis (XLRS). *Methods*: XLRS was diagnosed clinically and corroborated with full field ERG and optical coherence tomography. Eight eyes of four patients underwent mfERG using the VERIS 5.2.1X system following the ISCEV guidelines. The mfERG stimulus array consisted of 103 hexagons flickering according to a pseudorandom m-sequence with a mean luminance of 100 cd/m^2. The first order kernels obtained from six concentric rings were analyzed. The N1 and P1 waveform amplitudes and implicit times for each ring were compared between the patients and normals. The average of the P1/N1 amplitude ratio of each ring of each eye of patients was compared with the b/a amplitude ratios of the maximal combined, cone and 30 Hz flicker responses. *Results*: N1 amplitudes were significantly affected in all the rings ($P < 0.0001$ in rings 1 and 2, $P < 0.0007$ in ring 3, $P < 0.0034$ in ring 4, $P < 0.0023$ in ring 5 and $P < 0.002$ in ring 6). P1 amplitudes were significantly affected in all the rings

($P < 0.0001$ in all rings). Though P1 implicit times were significantly affected in all the rings; N1 implicit times were significantly affected only in the outer four rings. The average P1/N1 ratios were not comparable to the b/a ratios. However, this ratio approached closest to the b/a ratio cone of the full field cone ERGs. *Conclusions*: In X-linked retinoschisis significant reduction is seen in mfERG amplitudes of N1 and P1. MfERG can provide insight into the functional changes in the retina in X-linked retinoschisis.

Poster A3. Objective analysis of macular function in HIV-positive children without infectious retinitis. An OCT and multifocal ERG study

Marilita M. Moschos, Michael Apostolopoulos, Chronis Minogiannis, Tryfon Rotsos, Spyridon Papadimitriou, Michael Moschos
Department of Ophthalmology, University of Athens, Greece

Purpose: To evaluate objectively by mfERG and OCT the macular function in children with human immunodeficiency virus (HIV) disease without cytomegalovirus retinitis or visual symptoms. *Methods*: We examined 38 eyes of 19 HIV-positive children (group A) with no history of ocular disease or eye surgery and no subjective symptoms. Patients in group B (40 eyes of 20 patients) were HIV-negative age-matched control subjects. Each individual underwent a complete ophthalmic examination, OCT-3 scan and mfERG recording. *Results*: The mean foveal thickness measured by OCT in groups A and B was 190.28 μm (±26.58 SD) and 169.47 μm (±10.17) respectively and the difference was considered significant ($P = 0.00001$). The mean retinal response density of mfERG of the fovea in groups A and B was 19.87 nV/deg^2 (±4.59) and 22.02 nV/deg^2 (±0.9) respectively and the difference was statistically significant ($P = 0.008$). The mean retinal response density of the parafovea in groups A and B was 10.82 nV/deg^2 (±2.34) and 12.23 nV/deg^2 (±0.547) respectively and the difference was statistically significant ($P = 0.001$). *Conclusion*: Our study shows in some cases a significant thickening of the fovea and a significant decrease of the electrical activity of the foveal and parafoveal area in human HIV-positive children with no visual impairment or retinitis. This leads us to conclude that, in HIV-positive children apart from the ganglion cells, there is damage to the outer retinal layers and the photoreceptors. These findings are very important in the diagnosis of early subclinical HIV-associated visual loss.

Poster A4. Role of multifocal ERG (mfERG) in Stargardt's macular dystrophy

Ramakanth Reddy Kankara, Parveen Sen, Priya Ravi
Sankara Nethralaya, Medical Research Foundation, Chennai, India

Purpose: To explore the role and diagnostic value of multifocal electroretinogram (mfERG) in patients with Stargardt's Macular Dystrophy (SMD). *Methods*: Stargardt's macular dystrophy was diagnosed based on history and typical fundus findings of symmetrical bilateral involvement corroborated with full field ERG. Fluorescein angiography and visual fields were done if necessary. MfERG was recorded using a VERIS TM Science 5.1 System (Electro diagnostic imaging, EDI) developed at the Smith-Kettlewell Eye Research Institute in San Fransisco, California with 103 hexagonal stimulus arrays, from 20 patients with Stargardt's macular dystrophy and age-matched normal subjects to determine the electroretinographic responses in the central visual field. The N1 and P1 waveform amplitudes and implicit times of the patients and normal age-matched controls were compared at the various retinal eccentricities. *Results*: In all 20 patients with SMD the N1 and P1 amplitudes of the mfERG waveform were markedly diminished or non-detectable in the central retina 0°–18° when compared to peripheral retina, assuming a typical crater-like appearance in 3D topographic maps. N1 amplitudes were significantly affected in all the rings ($P < 0.0001$ in rings 1–4, $P < 0.001$ in ring 5, $P < 0.06$ in ring 6). P1 amplitudes were significantly affected in all the rings ($P < 0.0001$ in rings 1–4, $P < 0.001$ in ring 5, $P < 0.106$ in ring 6.) N1 implicit times were also delayed in all the eccentricities, however the delay was statistically significant in rings 4 & 5 ($P < 0.01$ in ring 4 and 0.02 in ring 5). P1 implicit times were also delayed in all eccentricities, however the delay was statistically significant in rings 2–5 ($P < 0.032$ in ring 2, $P < 0.001$ in ring 3, $P < 0.000$ in ring 4, $P < 0.006$ in ring 5). *Conclusions*: MfERG is a novel technique very useful in detecting foveal dysfunction in SMD. Multifocal electroretinography yields local resolution of the electrical retinal activity evoked by light stimuli, in contrast to the summed response in conventional ganzfeld ERG. MfERG in SMD helps to quantify, prognosticate and monitor the foveal dysfunction.

Poster A5. The recording sensitivity of multifocal electroretinograms (mfERGs) in patients with retinitis pigmentosa

Yong Liu, Zheng Qin Yin, Yanji Yu, Xiao Hong Meng
Southwest Eye Hospital/Southwest Hospital, Third Military Medical University, Chongqing, China

Purpose: To investigate the recording sensitivity of mfERG in patients with retinitis pigmentosa (RP) and to analyse the predictive factors for recordable or non-recordable mfERG. *Methods*: Patients with RP and visual acuity (VA) ranging between 0.2 and 1.0 log MAR were included. All patients underwent mfERG testing (103 hexagons, and luminance of 200 cd/m^2), static perimetry, fundus photography and fundus fluorescence angiography. First-order kernel mfERG was analyzed for total noise, signal-to-noise ratio (SNR), response amplitude, and implicit time. The number of identified valid mfERGs were counted and compared with VA, visual field (VF), retinal artery diameter, bone-spicule pigmentosa area. *Results*: Eleven patients aged 14 to 56 were included. MfERGs were successfully performed in 8 of 11 patients. In all stimulated areas, 17.3% waveforms were determined to be valid responses using SNR criteria. The VA of patients with non-recordable mfERGs was 0.3, 0.6, and 0.6 respectively. The numbers of recordable mfERGs were not associated with VA and retinal artery diameter. Bone-spicule pigmentosa area and the VF can be sensitive enough to predict recordable mfERGs. *Conclusion*: Recordable mfERG in patients with RP were not associated with VA but with the bone-spicule pigmentosa area and VF. Neuro-sensory retina was destroyed by bone-spicule pigmentosa and this may induce an epileptic-like abnormal electric signal.

Poster A6. The use of multifocal electroretinography (mfERG) in occult macular dystrophy

Jasmine W. S. Ngai[1], Timothy Y. Y. Lai[2], Carmen K. M. Chan[1], Dennis S. C. Lam[2]
[1]Hong Kong Eye Hospital, Hongkong;
[2]Dept of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong

Purpose: Occult macular dystrophy (OMD) is an unusual macular dystrophy causing progressive central vision loss with normal fundus appearance and with normal fluorescein angiographic and full-field electroretinography (ff ERG) findings. We describe the clinical characteristics, ffERG and mfERG findings in six patients with OMD. *Methods*: Six patients with OMD were characterized clinically and electrophysiologically. MfERGs were recorded using VERIS system with 103 and 61 hexagonal elements in five patients and in one patient respectively. Trace arrays and three-dimensional plots were presented and compared with those of normal controls. *Results*: Most patients presented with normal fundus appearance and the ff ERG were normal in all patients. MfERG demonstrated significant reduction in first-order kernel response amplitude at the central macula in all patients and allowed a diagnosis of OMD. *Conclusions*: MfERG is a valuable tool in the diagnosis of OMD as other investigations including fluorescein angiography and full-field ERGs are normal in these patients.

Poster A7. To analyze the naso-temporal disparity of multifocal ERG (mfERGs) in patients of advanced glaucomatous field defects

Ajoy Vincent[1], Rohit Shetty[1], A. V. Sathidevi[2], S. Anita[2]
[1]Department of Electrophysiology, Narayana Nethralaya, Banguluru, India; [2]Department of Glaucoma Services, Narayana Nethralaya, Banguluru, India

Purpose: To assess first order kernel responses of mfERG in patients with documented severe glaucomatous field defects for the assessment of naso-temporal disparity. *Methods*: Twenty-nine glaucomatous eyes of 29 patients underwent complete ophthalmological evaluation including best corrected VA, IOP, C/D ratio, 30-2 HFA and Optical Coherence Tomography (OCT). Patients diagnosed to have advanced field defects on HFA underwent 37B mfERG following ISCEV guidelines with mean luminance of 100 cd/m^2 with a contrast of 95%. Twenty-nine eyes of normal healthy hospital volunteers served as controls. N1 amplitude and latency, P1 amplitude and latency were analyzed for naso-temporal disparity in both the groups. *Results*: N1 and P1 amplitudes in both groups did not show any statistical difference between nasal and temporal locations. N1 and P1 latency showed mild difference in normals. In glaucomatous patients, N1 and P1 latency difference improved. However when an individual analysis was done, 10 eyes still showed naso-temporal disparity. However the mean OCT thickness in these patients did not show a significant difference compared to that of the other eyes. *Conclusion*: Optic nerve component is partly responsible for naso-temporal disparity. The disappearance of naso-temporal disparity did not directly correlate to amount of nerve fibre loss. Hence other factors also contribute to naso-temporal disparity in mfERGs.

Poster A8. Evaluation of retinal function in retinitis pigmentosa and occult macular dystrophy using reading acuity, contrast sensitivity and multifocal electroretinogram

Manami Kuze, Hisashi Matsubara, Yukitaka Uji
Department of Ophthalmology, Mie University School of Medicine, Tsu, Japan

Purpose: To evaluate the relationships among visual acuity, reading acuity, contrast sensitivity (CS) and multifocal electroretinogram (mfERG) in patients with retinitis pigmentosa (RP) or with occult macular dystrophy (OMD). *Methods*: In 18 eyes of nine patients with RP and 10 eyes of five patients with OMD, we measured the best-corrected distance vision acuity (VA). MfERG was recorded at 103 discrete retinal locations using VERIS (Mayo, Japan) and the critical print size (CPS) was determined with the Japanese version of the Minnesota reading chart (MNREAD-J Chart). CS was examined using CA2000 (Neits, Japan). *Results*: The mean mfERG implicit times of responses from the central 10° area, shortened by 3.1 in RP and were delayed by 1.2 ms in OMD compared to those of the peripheral area. VA (log MAR) was RP: 0.24 + /– 0.05, OMD: 0.27 + /– 0.13. CPS (log MAR) was CD: 0.38 + /– 0.01, OMD: 0.56 + /– 0.09. CS decreased more remarkably in day vision in comparison with night vision in patients with OMD, while CS decreased both at day and night in RP patients. In eyes with RP, the correlations between VA and CPS were statistically significant ($r = 0.98$, $P < 0.001$), as also between VA and CS ($r = 0.70$, $P < 0.001$). However, the correlations between VA and CPS, VA and CS did not reach statistical significance in OMD. *Conclusions*: Visual impairment is revealed by CS and CPS both in RP and OMD; however it is independent of VA in OMD. Eyes with OMD showed more severe visual dysfunction than expected from VA.

POSTER SESSION 1. Group B. Frontiers in Electrophysiology Techniques

Poster B1. Retinoschisin gene transfer therapy alters the natural history of retinal degeneration in Rs1h-KO mouse and gives long-term rescue

Sten Kjellstorm, Ronald A. Bush, Yuichiro Takada, Yong Zeng, Paul A. Sieving
NEI/NIDCD/NIH, USA

Purpose: Characterize the natural history of the Rs1h-KO mouse as a model for human x-linked retinoschisis (XLRS) and evaluate the long term effects of retinal rescue following AAV(2/2)-CMV-Rs1h gene delivery. *Methods*: Full-field scotopic electroretinograms (ERGs) were recorded from 44 male hemizygous Rs1h-KO and 44 male wild type C57BL/6J (WT) mice at six ages between 1 and 16 months. Retinal morphometry included outer segment layer (OSL) width, photoreceptor cell count and grading of schisis cavity severity. One eye each of p14 RS-KO mice was injected with AAV (2/2)-CMV-Rs1h, and retinal histology and ERGs were analyzed out to 14 months. *Results*: At 1 month of age the outer nuclear layer (ONL) of Rs1h-KO mice was disorganised but had nearly normal cell counts. The OSL was thinned, rod outer segments were misaligned, and abundant schisis cavities spanned the inner nuclear and outer plexiform layers in all retinas. The ERG a- and b-wave amplitudes at this age were reduced by 33% and 50%, respectively. The ERG and ONL cell number decreased further between 1 and 16 months with unequal changes in the a- and b-waves with age. The a-wave reduction correlated well with the steady decline in ONL cell number, while a rapid decline in the b-wave and b/a-wave ratios less than in WT were associated with increasing severity of schisis cavities at young ages. At 4 months the cavities were maximal but coalesced and disappeared at older ages. The b/a-wave ratio was inversely correlated with cavity severity across all ages ($r = –0.74$, $P < 0.0001$, $n = 22$). Considerable heterogeneity was observed at each age in the ERG amplitudes and retinal morphology. Mice injected with AAV-Rs1h at 14 days showed considerable structural and functional rescue at 14 months, including improved rod outer and inner segment integrity, less photoreceptor cell loss and larger ERG amplitudes compared to untreated fellow eyes. *Conclusions*: The ERG of the Rs1h-KO mouse at early ages reflects disruption of both photoreceptor and second-order neuron function. In mid- to late-ages the ERG decline reflects primarily photoreceptor degeneration. The Rs1h-KO mouse is consistent with human clinical XLRS in showing schisis cavities, which affect primarily the b-wave, the regression of schisis cavities at older ages and a considerable range in phenotypic severity across individuals. This mouse model also indicates the critical roll of RS-protein in photoreceptor survival consistent with decreased a-waves in some XLRS-patients. Long-term rescue of retinal morphology and function by AAV-Rs1h gene transfer may provide a basis for considering intervention in the homologous human XLRS condition.

Poster B2. Electrophysiological evidence for heterogeneity of lesions in optic neuritis

A. Klistorner[1], S. Graham[1], C. Fraser[1], R. Garrick[1], T. Nguyen[2], M. Paine[2], J. O'Day[2], J. Grigg[1], H. Arvind[1], F. C. Billson[1]
[1]Department of Ophthalmology, Save Sight Institute, University of Sydney, Sydney; [2]Center for Eye Research, Melbourne University, Melbourne, Australia

Purpose: Optic neuritis (ON) represents a good model to examine the process of myelin destruction and repair because the effects are clinically apparent and measurable. It is believed that amplitude of full-field visual evoked potential (VEP) reflects axonal degeneration while delayed conduction reflects demyelination of the optic nerve. The multifocal VEP (mfVEP) provides a breakdown into locally derived VEP responses and can map both the amplitude and latency of multiple sites up to eccentricity of 24 degrees. The purpose of this study was to examine serial mVEP changes in patients with acute optic neuritis. *Methods*: MfVEPs were performed using the Accumap^{TM}, which employs a cortically scaled dartboard pattern with 58 segments. Patients with newly-diagnosed, acute unilateral ON, MRI changes consistent with demyelination, and no previous diagnosis of multiple sclerosis were prospectively enrolled and followed up for 1 year with serial mfVEP recording. Amplitude and peak latency were analysed using traces derived from stimulation of individual segments. *Results*: 27 subjects were enrolled. In 5 patients, amplitude did not recover significantly, or deteriorated after initial recovery so that latency could not be measured. This possibly reflects extensive axonal loss. In 22 patients, amplitude recovered in 1 month sufficiently to permit serial latency analysis. Averaged latency of affected eye was significantly delayed compare to non-affected eye ($P < 0.00001$). Latency asymmetry between affected and non-affected eyes at 1 month after acute ON was 31.5 ($\pm$7.7SD, range 19–46) ms. Six out of 22 patients (27%) did not show any noticeable latency improvement over the follow-up period, possibly reflecting failure of remyelination. In the remaining cases (16 patients, 73%) latency demonstrated considerable improvement (55.4 $\pm$ 12.6%, $P = 0.029$ one-way ANOVA) suggestive of remyelination. *Conclusion*: Using mfVEP, it is possible to distinguish between optic neuritis cases with extensive axonal loss and different patterns of myelin repair.

Poster B3. The techniques and system for retina scan

Aram H. Arakelyan[1], Mineo Kondo[2]
[1]Department of Information Technologies, University of International Economic Relations, Yerevan, Armenia; [2]University School of Medicine, Dept of Ophthalmology, Nagoya, Japan

Purpose: To develop a technique and system for retina brain scan targeted for investigation of retinal responses to colour and white and black stimuli taking into account the density of the allocation of rods and cones in the retina. *Methods*: The testing method is based on the following approaches: (a) For mfERG the value of the radius of circle formed by hexagonal segments is first set up. Then the values of the width of the rings sequence formed by hexagonal segments are set up, after which the stimulus generation according to the linear recurring a-sequences (LRAS) is implemented. LRAS provides the change of colours of two hexagons during each step of stimulus generation. These hexagons are symmetric relative to the central hexagon. The sequence of hexagon rings is initiated from the central circle; (b) For PERG and VEP the size of the central checkerboard and the size of the square pattern area formed by a band of these are checked. The stimulus generation according to the sequential selection of central checkerboard and then the generation of square pattern area is implemented; (c) for mfVEP the value of the radius of central circle of checks and size of the sequence of check segments are setting up. The stimulus generation according to the sequential selection of central checkerboard and then the generation of sequence of check segments is implemented. Because cones and rods have different sensitivities to stimulus colours, the new method allows generation of continuous (colour background and colour flash, black background and white flash) stimulation sequences selectively depending on the density of the allocation of rods and cones in the retina. *Results*: The stimulator we developed allows stimulation of the retina depending on the density of allocation of rods and cones in retina. Listed features substantiate the fact that new methods of stimulus generation are unique and different than that of others and could be used as the basis for a new technology in clinical electrophysiology and neurophysiology of vision. The software provides for the selection of a defined number of hexagons in each area and for generation of flashes of specified frequency and duration according to the automatically selected options. Algorithms of the stimuli generation are based on linear recurring a-sequences (LRAS). The diversity of LRAS allows a choice between existing different classes and so recording retina responses to these stimuli. Consequently, it is also possible to receive multifocal images as responses to stimuli. *Conclusions*: Developed techniques of mfERG, PERG, VEP and mfVEP are a promotion of existing methods and could be used in clinical practice.

Poster B4. Objective evaluation of the difference in blur sensitivity by the pattern VEP between myopes and emmetropes

Xiao-Ling Liu
Wenzhou Medical College, Wenhou, China

Purpose: The purpose of this study is to use the transient pattern visually evoked potentials (PVEP) to objectively evaluate the blur sensitivity and compare the difference between emmetropia and myopes. *Methods*: Thirty-four subjects were classified into two groups: 14 emmetropes (mean refractive error –0.07 (±0.28) D) and 20 myopes (mean refractive error –3.73 (±0.85) D). The age range was 18–28 years. Testing was conducted monocularly (oculus dominans). The subject wore his/her best correction. PVEPs were recorded under six defocus conditions: 0, +0.25 D, +0.50 D, + 0.75 D, +1.00 D and +1.50 D. The subjects' transient PVEPs were recorded to contrast-reversing checkerboard patterns (10 visual angle, 97% contrast, 1 Hz) using the Roland system. Amplitude and latency of the PVEP were measured for each defocus condition. *Results and conclusions*: A regression line was used to fit the amplitude data plotted versus the defocus values for each subject and then the slope represented the sensitivity of the subject to image defocus on the retina. The average slopes for emmetropes and myopes were –7.66 ± 1.97 (SD) (μv/D) and –5.74 ± 0.93 (SD) (μv/D), respectively. The difference in the slope between the emmetropes and myopes was significant ($P < 0.01$). Based on the data, individuals with myopia are less sensitive to retinal defocus or the presence of blur than individuals with emmetropia.

Poster B5. Retinitis pigmentosa (RP) a dual genetic and autoimmune disease. An hypothesis with therapeutic implications

Alfred T. Sapse
Stem Cell Pharma Inc, USA; Stem Cell King Pharma Pvt. Ltd, India

Purpose: To provide evidence for the hypothesis that retinitis pigmentosa (RP) is a dual disease, genetic and autoimmune, as expressed through the presence of retina antibodies and the immune suppressive hormone, cortisol. *Method*: Instituting a dual approach to treat RP, through the use of embryonic stem cells to repair or replace the damaged rod photoreceptor cells and controlling cortisol through cortisol modulating agents. *Results*: Nine patients with RP have been treated so far, and followed up for periods ranging from 1 to 5 months. The subjective improvements ranging from mild to impressive were recorded. Changes in post-operative ERG and visual status as compared to the preoperative status will be presented. *Conclusion*: RP improvements that can occur after this treatment support, but do not validate, the genetic/autoimmune hypothesis. Additional RP treatments are needed before a more conclusive opinion can be drawn.

Poster B6. Vision in depressive disorder—assessing contrast vision with the pattern ERG and VEP

Elena Kern[1], Emanuel Bubl[1], Michael Bach[2]
[1]Department of Psychiatry, University of Freiburg, Germany; [2]Department of Ophthalmology, University of Freiburg, Germany

Introduction. Altered contrast sensitivity has been reported in different neurological and psychiatric disorders. It was differentially affected in dopamine deficiency diseases like Parkinson's disease compared to diseases with a dopamine surplus as seen in schizophrenia. We here used the pattern ERG (PERG) and the VEP to assess contrast processing in the retina and in the visual cortex of depressed patients, where a reduced dopaminergic transmission is thought to be involved in the pathophysiology. *Methods*. We examined 20 patients with a diagnosis of major depression and 20 age-matched control subjects without any psychiatric disease. All subjects were optimally refracted for the stimulation distance of 57 cm; their visual acuities were 0.9 or higher. Subjects viewed checkerboard stimuli of 0.8° check size, square-wave reversing at 12 rps with a luminance of 45 cd/m^2. Fixation was monitored via small digits appearing at the fixation cross, to be reported by the subject. Contrast levels covered 3, 7, 16, 36, and 80%. A veridical (noise free) response estimate and its significance level were calculated using Fourier analysis. The contrast threshold was defined as the lowest contrast level producing a significant response in the PERG or VEP. *Results*. PERG contrast transfer functions were monotonic and nearly linear versus linear contrast for all subjects. VEP contrast transfer functions had a high inter-individual variability and often did not rise monotonically with contrast. Fixation accuracy and the number of artifacts were comparable for both groups. Comparing contrast thresholds across groups, we found the PERG threshold significantly elevated in the depressive patients (60.1 ± 22.5% versus 24.1 ± 11.4%, $P < 0.01$). No significant group difference was observed for the VEP. *Conclusions*. The marked findings in the PERG point at retinal changes in depression, possibly mediated via dopamine. We

hypothesize that changes in the VEP are also present but reduced by contrast gain in the LGN and swamped by the high variability. The unexpectedly clear results even suggest use of the PERG as a possible surrogate marker to assess single patients with mood disorder.

Poster B7. Can event related potentials (ERPs) be used as an objective measure of stereopsis?

Uma Shahani[1], Neville Prescott[1], Lynne Watson[1], Velitchko Manahilov[1], Petar Mihaylov[1], W. S. Simpson[2]
[1]Vision Sciences, Glasgow Caledonian University, UK; [2]School of Psychology University of Plymouth, UK

Purpose: To ascertain if ERPs could be used as an objective measure of stereopsis. *Methods*: Sixteen adult subjects (eight stereo-normal and eight amblyopic) consented to the study carried out in accordance with local ethics committee guidelines. The stimuli were dynamic random dot stereograms (dRDS) continuously displayed and comprising either flat fusion to depth, rivalry to flat fusion or rivalry to depth during periods of 500 ms pre-stimulus, 500 ms triggered and 500 ms post-stimulus. The experiments looked at fusion with no depth (correlated red/green dots) to induced depth (Dyn 1); flat fusion (superimposed red/green dots with no disparity) to induced depth (Dyn 2); rivalry (uncorrelated red/green dots) to flat fusion (Dyn 3); rivalry to induced depth (Dyn 4). Perceptually, the coherent 3D stimulus appeared as horizontal sinusoidal gratings of two cycles per screen. ERPs were recorded using 32 active electrodes (BioSemi inc) in a modified 10–20 system array with four additional electrodes to monitor eye movements. Three midline electrode sites (Oz, POz and Pz) were chosen and analyzed. Control experiments comparing crossed and uncrossed disparity and optical blurring of the stimulus in normals were also carried out. Monocular and binocular VEPs to a reversing checkerboard (30′ of arc) were recorded as a standard. *Results*: N1 amplitude remained unaffected by amblyopia over Oz. Amplitudes of N2 and P3 peaks were significantly greater ($P < 0.001$) in normals than in amblyopes for all stimulus conditions and over all three sites. N1 peak amplitude at POz and Pz was greater for strabismic amblyopes than for anisometropic amblyopes while this was reversed for N2. The anisometropes showed a significantly delayed N2 at POz ($P = 0.03$) relative to the strabismics. Monocular optical blurring in normal subjects did not have any effect on the resultant ERPs. *Conclusions*: The significantly larger amplitudes of ERPs elicited by dRDS in normal subjects compared to those of amblyopes did provide a physiological correlate of induced disparity. ERPs from strabismic and anisometropic amblyopes elicited by the same stimuli were significantly different from each other. This suggests that their visual processing of disparity may not be the same.

Poster B8. Changes of pattern electroretinograms after transcorneal electrical stimulation

Kazuha Ogata
Department of Ophthalmology and Visual Science Chiba University Graduate School of Medicine, Chiba, Japan

Purpose: Electrical stimulation of the transected optic nerve stump is reported to have enhanced the survival of retinal ganglion cells (RGCs) in rats. It was also reported that transcorneal electrical stimulation (TES) improved visual function in patients with optic neuropathy. The purpose of this study was to examine the changes of the pattern electroretinograms (ERGs) after TES to evaluate effects of TES on RGC function in normal healthy subjects. *Methods*: TES was delivered through a bipolar contact lens electrode with biphasic electrical current (20 Hz, 400 μA) in 10 normal healthy subjects. Pattern ERGs were elicited by checkerboard stimuli and recorded before and immediately after TES. *Results*: There was no significant difference in the amplitudes and implicit times of both P50 and N95, between before and immediately after TES. *Conclusions*: These findings suggest that TES does not affect the function of normal retinal ganglion cell and the optic nerve at least.

Poster B9. Visual behaviour evaluation in a live animal model for surgical training

Sarbani Hazra[1], Dipak Kumar De[1], Arup Kumar Bose[2], Biswarup Roy[3], Aditya Konar[4]
[1]Department of Veterinary Surgery & Radiology, West Bengal University of Animal & Fishery Sciences; [2]Eye Microsurgery and Laser Center, Chinsura, Hooghly; [3]Department of Ophthalmology, R.G. Kar Medical College and Hospital, Belgachia; [4]Indian Institute of Chemical Biology Jadavpur, Kolkata, India

Purpose: To assess the visual and surgical outcome in a new live model for surgical training. *Methods*: Cataract was induced in the left eye of each dog by puncturing the anterior capsule of the lens through the limbal approach, using the bevelled end of a 26-gauge needle, under general anaesthesia. Phacoemulsification was performed in all the eyes following development of cataract. Development of cataract and return of vision after surgery was assessed

by standard subjective tests for vision, i.e., the cotton ball test and the maze test. *Results*: Ophthalmologic examination showed that posterior cortical opacification started from day 5 to 7 post induction and complete cataract formation was observed by 75 days post induction. With increasing cataract the vision as assessed by the functional tests showed deterioration. Restored vision was assessed in all patients using behavioral tests. The tests showed vision was restored in all the dogs following phacoemulsification. *Conclusion*: Considering the enormous losses caused initially by inexperienced surgeons while performing phacoemulsification, this live model should be far superior to the common practice of training in phacoemulsification using cadaver eyes. The visual function tests developed for the dog can help to assess loss and restoration of vision after eye surgery in live dog models.

Poster B10. Diurnal and inter-test variation in pattern electroretinogram

Subhadra Jalali[1], P. Bhanu Rakesh Varma[1], L. S. Mohan Ram[1], Sannapaneni Krishnaiah[2]
Smt. Kanuri Santhamma Centre for Vitreoretinal Disease, L.V. Prasad Eye Institute, Hyderabad, India; [2]ICARE, L.V. Prasad Eye Institute, Hyderabad, India

Purpose: To assess the diurnal and test-retest variation of pattern electroretinograms (PERG) using LVP electrode in normal subjects. *Methods*: Multiple transient PERG using pre-defined standard parameters were recorded in 23 male and 2 female healthy volunteers with mean age of 21.5 years. LVP electrode was used in all eyes. Five recordings at predetermined time-slots, over 24 h, were done for each subject to assess diurnal variation. The PERG was also repeated in all individuals to assess the reproducibility, and in 10 individuals on different days to assess inter-test variability. The amplitudes and implicit times for N35, P50, and N95 were tabulated by a masked observer. *Results*: PERG data from 50 eyes of 25 patients was analysed. The mean peak latency in milliseconds was 27.9 ($\pm$1.44 SD) for N35, 51.1 ($\pm$2.0) for P50 and 95.3 ($\pm$12.4) for N95 components. Mean amplitudes respectively were –1.55 ($\pm$1.48), 6.78 ($\pm$4.47) and –8.83 ($\pm$4.95) mV. For repeat measurement at the same time-interval, the corresponding latency variances were 2.10, 2.34 and 3.46 giving an overall 3–5% variance, which was not significant clinically. The corresponding diurnal recordings had variance values of 2.41, 3.44 and 8.34 (3–6% variance overall). For amplitudes, the inter-test variability was 0.76, 2.48 and 4.59 while diurnal variance was 0.85, 6.74 and 10.18 (43–47% variance for both). Tests for intra-class coefficient of variation showed significance values >0.05 for all groups for the F test for peak latency measurements but <0.05 for amplitudes. This identified no significant diurnal or test-retest variability for peak latencies but clinically significant variance for amplitudes. The variance is comparable to earlier studies in literature. *Conclusion*: Peak latency measurements of PERG showed no clinical or statistically significant diurnal or test–retest variability. Amplitude measurements showed significant variation as expected.

Poster B11. Longitudinal assessment of vision in prematurely-born children with cerebral visual impairment (CVI) over the ages during which vision typically matures

Anne Moskowitz, Janet S. Soul, D. Luisa Mayer, Jacqueline M. LeMoine, Ronald M. Hansen, Anne B. Fulton
Department of Ophthalmology, Children's Hospital and Harvard Medical School, Boston, USA

Purpose: To study the development of vision in prematurely born children with cerebral visual impairment (CVI) over the ages during which vision typically matures. *Methods*: Longitudinal measures of vision were obtained in 12 prematurely born children (gestational age 26 to 34 weeks; median 31 weeks) using electrophysiological and behavioural techniques. Subjects presented with bilateral visual loss in the presence of normal ocular structures and intact pupillary light reflex. All had severe cerebral white +/– gray matter injury associated with prematurity. Measures of grating acuity were obtained from each subject using sweep visual evoked potential (VEP) and preferential looking (PL) procedures at three or more ages (median: 6 VEPs, 10 PLs). In addition, an overall functional vision score was derived by evaluating attention, perception, and visual-motor capabilities. For each subject, the courses of VEP and PL acuity development were compared with normal development. Measures of visual acuity and functional vision were evaluated for significant relationships. *Results*: In all subjects, both VEP and PL grating acuity were below normal for age. VEP acuity was better than PL acuity by a factor of four (twice the average difference found in normal development). VEP acuity increased in all 12 subjects; PL acuity increased in nine and remained stable in three. In children whose acuity increased, the rate of improvement (~0.3 octave/year for both tests) was lower than normal (VEP ~0.5 octave/year; PL ~0.6 octave/year). Although parallel courses of VEP and PL development occurred in most subjects, substantial disparities were observed in a few. Functional vision score was significantly correlated with final VEP acuity ($r = 0.64$; $P < 0.05$) but not with

final PL acuity ($r = 0.30$, ns). *Conclusions*: Despite significant cerebral injury, vision improved in these prematurely born children; none worsened. In this sample, functional vision was correlated with final estimates of electrophysiological (VEP) but not behavioural (PL) acuity.

POSTER SESSION 2. Group C. Clinical Cases and Case Series

Poster C1. An adCSNB Chinese family and its electroretinogram characteristics

Xiao-ling Liu
Wenzhou Medical College, Wenhou, China

Purpose: To report the electroretinogram (ERG) characterization of a large twelve-generation Chinese family with autosomal dominant congenital stationary night blind (adCSNB). *Methods*: The family members were examined for clinical characteristics, electrophysiological evaluation, dark adaptometry and mutation study. *Results*: Forty affected individuals (16 female and 28 males) were detected in this Chinese family. The affected patients exhibited no progressive night blindness and normal day vision from birth. The ERG recording (following ISCEV standard) of eight affected individuals in this family revealed severely diminished b-wave responses to dim light stimuli (scotopic response), relatively normal a-wave and subnormal b-wave response to standard light stimuli. In addition, the OPs and cone responses were mildly depressed. The dark adaptation curves of three patients showed a mono-phase curve, typical for night blindness. We have excluded the five previously known mutations in the three genes (RHO, PDE6B, and GNAT1) associated with adCSNB and linkage studies have excluded tight linkage between the disease locus and markers associated with these three genes. This family exhibits a different gene mutation from previously identified RHO, PDE6B and GNAT1. *Conclusion*: New genetic mutations for this adCSNB Chinese family are reported along with the clinical and ERG characteristics.

Poster C2. Cystoid macular oedema during pregnancy in patient with retinitis pigmentosa

Alma Patrizia Tormene, Elisabetta Pillotto, Chiara Riva
Ophthalmic Clinic of Padova University, Italy

Purpose: This case report describes a patient affected by retinitis pigmentosa (RP) sine pigmento who, in the seventh month of pregnancy, showed cystoid macular oedema (CME); the clinical evolution of the oedema was followed up until the tenth month after delivery. *Methods*: A complete ophthalmologic examination with electrophysiological, OCT and microperimetry examinations were carried out at onset of the symptoms, at 4 and 10 months after delivery. Electrophysiological exams (ERG including rod, maximal combined, cone and flicker responses) were performed with the applications of ISCEV standard recommended techniques using Mangoni equipment (Pisa Italy). Optical coherence tomography scanning of the fovea was performed using Stratus-OCT (Zeiss, Humphrey Instruments, Germany). Linear scans and fast macular thickness-based acquisition protocols were performed. A 10° area (3000 micrometers) centred onto the fovea was studied with microperimetry (MP1; Nidek Technologies, Padova, Italy). *Results*: At the seventh month of pregnancy visual acuity was 0.6 in RE and 1.0 in the LE. The retina presented narrowed vessels and, in the right foveal region, some cystic-like alterations were evident. ERG examination showed reductions in all the components. Foveal cystic-like spaces were evident on the OCT images in the right eye and foveal thickness was 340 μm. In the left eye fovea showed normal profile on OCT and foveal thickness was 144 μm. Microperimetry detected a reduction in foveal retinal sensitivity in the right eye, fixation was central but relatively unstable. In accordance with the patient's wishes, given her pregnancy, no therapy was carried out. Four months after delivery visual acuity had improved to 1.0 in RE, cystoid macular oedema was resolved on OCT images and foveal thickness was 152 μm. Retinal sensitivity had not improved significantly but microperimetry revealed that fixation had become central and stable. ERG examinations remained stable. Both clinical and functional aspects were unchanged 10 months after delivery. *Conclusions*: CME that appears during pregnancy in RP may go into spontaneous remission. There are various hypotheses regarding the aetiology and pathogenesis of CME in RP: alterations in the haemato-retinal barrier, an immune phenomenon, or a process of ischaemic origin. In the case of CME during pregnancy, it could be of a temporary nature and might go into spontaneous remission after delivery.

Poster C3. A case of acute blindness after taking quinine

Alma Patrizia Tormene, Chiara Riva
Ophthalmic Clinic of Padova University, Italy

Purpose: To describe the case of a 23-year-old woman, who, while undergoing treatment for suspected malaria,

presented acute signs of quinine poisoning after 3 days treatment (total consumed: 4.5 gm of the drug). Initially the symptoms were attributed to hysteria and only later was intoxication suspected. *Methods*: A battery of ophthalmologic examinations were carried out: Visual field and electrophysiological examinations (Visual Evoked Potential (VEP) Pattern reversal ERG (PERG), maximal combined ERG (MCR), ERG cone, flicker and rod responses, and an electro-oculogram (EOG)) on a woman who, 4 weeks earlier had completely lost her sight after taking 4.5 gm of quinine. Visual field examinations were carried out using a Humphrey perimeter 24-2 program. The electrophysiological tests were carried out according to ISCEV standards, using equipment from Biomedica Mangoni (Pisa, Italy). *Results*: When the patient was eventually examined, vision had returned (1.0 in both eyes), but she reported a reduction in the visual field. Analysis of the anterior segment revealed a wormlike movement of the iris and there was a generalised thinning of retinal blood vessels in the fundus. Visual field tests confirmed there was a concentric restriction and electrophysiological examinations revealed a reduction in PERG, above all in the P50-N95 ratio; normal VEP; electro-negative ERG MCR; and, an overall reduction in rod, cone and flicker responses. EOG was also reduced. *Conclusions*: Quinine can intoxicate the retina. It is thought that the damage is done by a vasospasm or by a direct toxic effect on various elements that make up the retina. Quinine would have a curare-like effect, interfering with the metabolism of acetylcholine. The curare-like effect would explain the worm-like movements of the iris. The electro negativity of ERG could lead one to suppose that the seat of the damage is post-transduction. Reductions in ERG rod, con and flicker responses and in the EOG reveal damage to photoreceptors and to the pigmented epithelium. Furthermore, the reduction in the N95 component of PERG reveals that the central retina is also involved especially the ganglion cells even though, when the tests were carried out, normal VEP showed that retino-cortical conduction had returned to normal.

Poster C4. Electrophysiological findings in dominant drusen—a case study

Priya R. Reddy, Praveen Sen, Bijoy K. Nair,
Kiran K. Daswani, Divya N. Nair
Sankara Nethralaya, Medical Research Foundation,
Chennai, India

Purpose: To report electrophysiological findings in patient with dominant drusen. *Methods*: A 27-year-old female came with a complaint of gradual decrease in distance vision over 6 months. The best-corrected visual acuity was 20/20, N6, in each eye. Colour vision as tested with the Ishihara pseudoisochromatic plates was normal. Fundus examination showed small round yellowish white drusen disseminated through out the posterior pole with foveal sparing. Full field and multifocal electroretinogram (mfERG) were recorded using VERIS 5.2.1 X, in accordance with the ISCEV standards. The mfERG stimulus array consisted of 103 hexagons, which subtended approximately 44° horizontally and 36° vertically at the viewing distance of 40 cm, flickering at a rate of 75 Hz according to a pseudorandom m-sequence. The first order kernel response densities were used to calculate the amplitude and implicit times of N1 and P1 responses. *Results*: Full field ERG showed normal rod driven responses and reduced and delayed cone driven responses when compared to age matched normals. MfERG showed a statistically significant reduction in N1 and P1 amplitudes for Ring 1 and Ring 2 responses without any significant delay in implicit times. Other ring responses also showed reduced amplitudes, but no statistical significance was found. In the left eye, the foveal peak was shifted to super temporal field indicating eccentric viewing. *Conclusion*: Dominant drusen revealed little change in the full field ERG in spite of widespread ophthalmoscopic changes but mfERG could objectively determine the extent of the functional damage.

Poster C5. Ganzfeld 30 Hz flicker ERG in diabetics

Gloria Wu, Matthew Severns, Jennifer Ha,
Radhika Sreeraman, Catherine Wang
Ophthalmology-Retina Vitreous, Los Gatos, CA, USA

Purpose: To determine if a 30 Hz flicker ERG shows retinal dysfunction in diabetics with mild diabetic retinopathy (DR). *Methods*: The implicit time of photopic 30 Hz flicker ERGs was measured for 27 eyes of 14 diabetic patients with VA < 20/40 and DR ranging from none to Stage 1 background DR. Controls were 39 eyes of 20 non-diabetics with VA < 20/40 and no macular disease or laser treatment. *Results*: 30 Hz flicker ERG was delayed in diabetic eyes (28.6 ± 2.0 ms) versus non-diabetic eyes (26.6 ± 1.7 ms, $P = 0.00015$, *t*-test). Statistical significance was unchanged after age correction. *Conclusions*: In diabetics with good visual acuity and mild retinopathy, 30 Hz flicker ERG shows abnormal inner retinal function. Such individuals should be followed up more closely than previously realized.

Poster C6. A case of Oguchi's disease without night blindness

Kaoru Fujinami[1], Kazushige Tsunoda[1], Kei Shinoda[2], Makoto Nakamura[3], Yoshihisa Oguchi[4], Yozo Miyake[5]
[1]National Institute of Sensory Organs, Tokyo, Japan; [2]Oita University, Oita, Japan; [3]Nagoya University, Nagoya, Japan; [4]Keio University, Japan; [5]Aichi Syukutoku University, Aichi, Japan

Introduction: Oguchi's disease, first described by Oguchi in 1907, is an unusual form of congenital stationary night blindness with an autosomal recessive inheritance. The SAG gene was first identified as a causative gene in 1995, and subsequently, mutations in the GRK1 gene were also found in 1997. We encountered a case of a Japanese patient presenting with a typical fundus appearance and Mizuo-Nakamura phenomenon but without night blindness. The ERG was only mildly affected. The genetic examination revealed a heterozygous mutation in the SAG gene. *Case report*: A 40-year-old-woman with fundus abnormality was pointed out in a clinical survey and consulted our hospital. She had no symptom of night blindness. The visual acuity was 20/20 in each eye. The fundus demonstrated a golden-yellow discoloration, and Mizuo-Nakamura phenomenon was observed after three hours of dark adaptation. The dark adaptation was delayed, but more mildly affected than in typical patients with Oguchi's disease. The mixed rod-cone ERG after 30 min of dark adaptation demonstrated a normal a-wave and slightly reduced b-wave with OPs. The amplitude of rod ERG was minimally reduced even with 30 min of dark adaptation. The cone and the 30 Hz flicker ERG were normal. No family history was found in her pedigree. Genetic examination revealed a heterozygous mutation of Asn309 (1-bp del) in the SAG gene, the most frequent causative mutation of Japanese patients with Oguchi's disease. No other mutation was found in the SAG gene as well as in the GRK1 gene. *Conclusion*: This is a first report, which shows a typical fundus characteristic of Oguchi's disease with only mildly affected ERG. A carrier with a heterozygous (Asn309 (1-bp del)) mutation in the SAG gene may present mild clinical features in Oguchi's disease. The result also indicates that golden-yellow discoloration of fundus does not correlate with ERG findings in Oguchi's disease.

Poster C7. Clinical and electrophysiological findings in a Wagner syndrome-like hereditary vitreoretinal degeneration with no detectable pathogenic mutations in the versican gene

Christoph A Amstutz[1], Elmar P Messmer[1], Barbara Kloeckener-Gruissem[2], Wolfgang Berger[2], Klara Landau[1]
[1]Department of Ophthalmology, University Hospital, Zurich, Switzerland; [2]Division of Medical Molecular Genetics and Gene Diagnostics, Institute of Medical Genetics, University of Zurich, Switzerland

Purpose: Wagner syndrome is a rare autosomal dominant disorder belonging to the group of hereditary vitreoretinal degenerations. It is characterized by myopia, a typical form of vitreous syneresis with translucent membranes scattered in an otherwise optically empty vitreous, and retinal detachment in some cases. Recently, CSPG2 encoding versican, a proteoglycan and extracellular matrix component of the human vitreous, has been identified to be the defective gene in Wagner syndrome. We describe the phenotype and the electroretinographic findings of an inherited vitreoretinal dystrophy similar to the Wagner syndrome phenotype with no pathogenic mutations in CSPG2. *Methods*: Four affected members of the family underwent clinical examination, including visual field examination and dark adaptation, and electroretinographic (ERG) investigations. Complete molecular analysis of the versican gene locus was performed. *Results*: The fact that the father, one daughter and two sons were affected (one other son was not affected) suggested an autosomal dominant trait for the disease. Moderate to high myopia was present in the affected family members. Best-corrected visual acuity and visual fields assessed by Goldmann perimetry were within normal limits, with the exception of functional impairment due to retinal detachment, occurring in three of the four affected family members. Circular vitreous strands and veils in the mid-periphery, and extensive areas exhibiting alterations of the retinal pigment epithelium were present in all affected family members. Full-field and multifocal ERGs and dark adaptometry revealed subnormal cone function, whereas the rod function did not seem to be affected. Mutation screening of the CSPG2 locus by DNA sequencing did not reveal any of the known pathogenic mutations or sequence alterations segregating with the phenotype. *Conclusions*: The reported phenotype with electrophysiologic abnormalities of the cone system and

no pathogenic mutations in the CSPG2 locus suggests an autosomal dominantly inherited vitreoretinal dystrophy different from Wagner syndrome.

Poster C8. Early changes in flash ERG in retinitis pigmentosa caused by a frame-shift mutation of the PRPF8 gene

Yujin Mochizuki, Atsushi Mizota, Minoru Tanaka, Akira Murakami, Hiroyuki Konda
Juntendo University Urayasu Hospital, Urayasu, Japan

Introduction: This study describes a Japanese family of autosomal dominant retinitis pigmentosa with a frame-shift mutation of the PRPF8 gene (IOVS, 2004). We report early changes in ERGs in this family. *Case report*: Case 1 was a 26-year-old man whose flash ERGs were extinguished when he was 4-year-old. Case 2 was a 20-year-old woman, the younger sister of Case 1. At 6 months of age, the amplitudes of her a- and b-waves of her flash ERGs were slightly reduced, and at 5 years, the ERGs were extinguished. Case 3 was the daughter of Case 2. The changes in her ERGs were extinguished at 1-year-of-age. *Conclusion*: In this family, the flash ERGs were extinguished at very young ages, similar to the reports describing patients with a mutation in the PRPF gene with early onset of symptoms. Simple flash ERGs are useful in the diagnosis of retinitis pigmentosa caused by a mutation of the PRPF8 gene in very young infants.

Poster C9. Functional changes of the retina in diabetes mellitus depending on the level of glycosylated haemoglobin

Mariam Arakelian[1], Yulla Bordeeva[2], Alla Ryabtseva[2], Angelika Shamshinova[1]
[1]Moscow Helmholtz Institute of Eye Disease, Moscow, Russia; [2]Moscow Regional Research Clinical Institute, Moscow, Russia

Purpose: The purpose of this study is to present the mechanisms of bioelectrical activity changes of the retina based on results of electroretinography (ERG) tests in patients with diabetes mellitus and high glycosylated haemoglobin (HbA1c). *Methods*: 25 patients (14 men and 11 women) with type I ($n = 15$) and type II ($n = 10$) diabetes who had much too high (8–10%) or extremely high (above 10%) levels of HbA1c were included in our study. All patients underwent standard ERG tests, as well as chromatic macular ERG to red, green and blue stimuli, oscillatory potentials (OP) in scotopic conditions (MBN, Russia). A RETIScan system for multifocal ERG (mfERG) was also used (Roland Consult, Germany). *Results*: Among the patients with type I diabetes (mean age 26.8 years) there were six newly diagnosed and four with long clinical course (from 12 to 15 years). They all had high visual acuity and showed no noticeable funduscopic changes. The maximal ERG was normal, flicker ERG was supernormal and the OP was increased. The b-wave amplitudes of chromatic macular ERG to red and green stimuli were slightly decreased. The amplitude values of mfERG were mostly decreased in paracentral areas at 11° to 30° of visual angle. Five patients with type I diabetes with duration of the disease from 8 to 15 years had moderate nonproliferative diabetic retinopathy with microaneurisms and "cotton-wool" spots. Two of them had extremely high levels of HbA1c > 11% and more significant lowering of bioelectrical activity of the retina compared with three patients who had level of HbA1c < 10% (8.7–9.9) and showed supernormal flicker ERG, increased index of OP but slight decrease of macular and mfERG amplitudes. In 10 patients (mean age 55.8 years) with type II diabetes (HbA1c > 7,5%) the duration of disease was from 6 to 12 years. They all had mild nonproliferative diabetic retinopathy; no significant changes of flicker ERG and OP were observed; macular and mfERG were subnormal ($P < 0,05$). *Conclusions*: The assessment of glycosylated haemoglobin is important in types I and II of diabetes mellitus for better understanding of metabolic disorders, which may determine the variability of the mechanisms of bioelectrical activity changes in the retina. Supernormal ERG might be an evidence of excitotoxic damage, causing neuronal hyperstimulation; at the same time, subnormal ERG may be due to focal retinal ischemia and a next stage of dystrophic changes of retinal cell structures. The role of glycosylated haemoglobin in complex chain reactions of retinal electrophysiology is still to be fully revealed.

Poster C10. Electrophysiological and psychophysical measures of pattern and motion sensitivity in patients with cone dystrophy

Karen Holopigian, Jenny M. Gallardo, Steven M. Hornik, Randolph Blake, Ronald E. Carr, William Seiple
New York University School of Medicine, New York, USA

Purpose: In previous work (Holopigian et al., ISCEV 2006), we found patients with RP could discriminate biological motion from random motion within normal limits at locations where performance on other

measures of visual function was abnormal. To further examine this effect, the current study looked at whether patients with central vision loss would be relatively unimpaired on a biological motion task. *Methods*: Eight patients with inherited progressive cone dystrophy were compared to an age-matched control group. The diagnosis was based on visual acuity, colour vision and local and full-field ERG results. For the patients, visual acuity ranged from 20/30 to 20/250. Contrast thresholds for drifting gratings and thresholds for detecting biological motion imbedded in noise were measured using a two AFC procedure. Thresholds were measured as a function of eccentricity (at the fovea, 6° and 12° temporal retina). Humphrey threshold visual fields and standard multifocal electroretinograms (mfERGs) were also obtained. *Results*: On the biological motion task, six of the patients were able to perform at normal or near normal levels at all eccentricities. At the same locations, contrast thresholds to drifting gratings were significantly elevated for seven of the patients. Likewise, mfERG parameters and Humphrey thresholds were significantly abnormal at these locations. In general, the mfERG parameters were poorest at the fovea and improved with eccentricity. In contrast, performance on the biological motion task and drifting grating task did not follow this pattern, nor did these measures correlate significantly with visual acuity. *Conclusion*: Consistent with the results in RP, the current study shows that patients with cone dystrophy performed well on a biological motion task where other measures were significantly abnormal. This implies that performance on the biological motion task may involve some higher-order processing that is not affected by the photoreceptor dysfunction that characterizes cone dystrophy.

Poster C11. Study of PERG before and after resolution of central serous retinopathy (CSR)

Jawahar Lal Goyal, Vishram Anil Sangit, Basudev Ghosh, Sushil Kumar
Guru Nanak Eye Centre, New Delhi, India

Purpose: To evaluate PERG changes before and after resolution of Central Serous Retinopathy. *Method*: Pattern ERG has three waves, a negative one at 35 ms (N35), a positive one at 45–60 ms (P50) indicator of macular function, and another negative wave at 95 ms (N95), which gives ganglion cell function. PERG was recorded using gold foil electrode and checkerboard pattern stimulus. Twenty patients with unilateral CSR were studied at presentation and at 6 weeks (after resolution). The fellow eye was taken as control. *Results*: At presentation, mean amplitude of P50 was 3.38 μV ($\pm$0.90 SD) in the normal eye as against 2.47 μV ($\pm$0.86) in the affected eye, reflecting a mean reduction of 26.7% in the P50 value indicating electrophysiological macular dysfunction. Mean N95 amplitude in the normal eye was 5.72 μV ($\pm$1.85) as against 4.27 μV ($\pm$1.66) in the affected eye with a mean reduction of 25.6% in the N95 amplitude indicating electrophysiological impairment of ganglion cell function. After resolution of CSR, the mean P50 value was 3.72 μV ($\pm$0.87) in the normal eye as against 3.24 μV in the affected eye ($\pm$0.94) with a mean reduction of only 13%. The mean N95 amplitude in the normal eye was 6.11 μV ($\pm$1.69) as against 5.69 μV ($\pm$2.21) in the affected eye with a mean reduction of only 6.69%. Improvement in amplitudes of P50 and N95 waves after resolution of CSR was statistically significant ($P < 0.05$ and 0.01 respectively) but it did not touch the normal level. Five out of 20 patients (25%) did not reveal any leak on FFA but PERG revealed abnormality suggesting that PERG is a more sensitive test. *Conclusion*: PERG is an important tool in the electrophysiological evaluation of cases of CSR and is more sensitive as compared to FFA.

Poster C12. ERG and VEP changes in sporadic Creutzfeldt–Jakob disease

Kazuhiko Tanabe, Atsushi Mizota, Minoru Tanaka, Toshihiko Oota, Reona Shimada, Akira Murakai
Juntendo University Urayasu Hospital, Urayasu, Japan

Purpose: Approximately 10% of patients with Creutzfeldt-Jakob disease (CJD) exhibit visual symptoms at presentation, e.g., decreased visual acuity, disturbance of eye movements, and defects of the visual field and approximately 50% of patients with CJD may develop such symptoms during the course of the disease. In the present report, we report changes ERGs and VEPs in a patient with sporadic CJD whose initial symptom was decreased vision. *Case report*: A 70-year-old man was referred to us with a complaint of decreased vision. He had had an ocular injury 3 years earlier to his left eye. At the initial visit, his visual acuity was 0.04 in his right eye and hand motion in his left eye. He had a mature cataract in his left eye. The a- and b-waves of the flash ERGs were reduced, and the peak latency of the P100 component of the VEPs was delayed. Electroencephalography showed 1 Hz periodic sharp wave complexes, which are typical for CJD. An increase in the concentration of neuron-specific enolase was detected in the cerebrospinal fluid (CSF), and CSF 14-3-3 brain protein was also present in the CSF. From these findings the diagnosis of CJD was made. *Conclusion*: The visual

electrophysiological tests provide an interesting noninvasive diagnostic tool for sporadic CJD.

Poster C13. Predictive value of visual evoked potential (VEP) in traumatic optic neuropathy

Ramesh Murthy
Department of Pediatric Ophthalmology
and Strabismus, Oculoplasty and Ocular Oncology,
LV Prasad Eye Institute, Hyderabad, India

Purpose: To evaluate the role of VEP in predicting visual recovery in traumatic optic neuropathy. *Methods*: A retrospective review of the records of patients with traumatic optic neuropathy presenting to our hospital. Visual acuity, concomitant orbital fractures and VEPs were studied. Steroids were given to patients who presented within 2 weeks of injury. Surgical management of the orbital fractures was done in selected cases. *Results*: A total of 14 patients were evaluated. Presenting visual acuity was 20/200 or worse in all cases. Improvement in the visual acuity occurred in 8 patients. Pattern VEP was extinguished in all except one where it showed reduced amplitude and delayed latency. Five of 9 patients who received intravenous steroids had an improvement in the visual acuity. Only 3 patients who had associated fractures of the orbital wall showed an improvement in vision. *Conclusions*: Pattern VEP at presentation does not appear to have a predictive value as regards the final visual recovery. Presence of associated fracture was associated with a poor prognosis. VEP is not a useful predictor of visual recovery in cases of traumatic optic neuropathy.

POSTER SESSION 2. Group D. Foundations of Electrophysiology

Poster D1. Establishment of normal ranges for the ISCEV standard electroretinogram

Enid Chelva, Doug Candy, John De Roach, Terri McLaren, Maribel Nosce, Roger Price
Sir Charles Gairdner Hospital, Nedlands, Australia

Purpose: This study was designed to examine the influence of age and gender on the normal ISCEV standard (2004) electroretinogram (ERG) in an effort to develop meaningful normal ranges for the test parameters. *Methods*: The ERG derived from HK-Loop electrodes was measured according to ISCEV standards following 45 min of dark adaptation and 10 min of light adaptation for scotopic and photopic studies respectively. The standard flash measured 1.8 cd s/m^2. Recordings from 60 normal volunteers, 32 (53%) females and 28 (47%) closely age-matched males, ranging in age from 6 to 87 with a mean of 44 ($\pm$20 SD) years, were made. Results from randomly selected eyes of each subject were used for analysis. *Results*: The rod b-wave implicit time was the only parameter strongly ($r = 0.72$) correlated with age, while amplitudes of the rod b-wave ($r = 0.53$), first wavelet of the oscillatory potentials ($r = 0.57$) and cone b-wave ($r = 0.53$) showed a moderately strong negative correlation with age. The combined rod-cone ERG a-wave ($r = 0.57$) and b-wave ($r = 0.60$) implicit times also showed a moderately strong correlation with age. There were no significant gender differences, with the exception of the b/a-wave ratio for the combined rod-cone response, which was significantly lower ($P < 0.05$) for the male population than for the females. None of the test parameters were normally distributed across the full age range, while analysis of the 30 closest neighbours for age described a natural delineation of ERG parameters into three age groups; below 40 years, 40–60 years, and over 60 years. *Conclusion*: In this study, ERG implicit times and amplitudes were shown to be affected by age, but not by gender, supporting the use of three separate age groups when compiling normal ranges.

Poster D2. Pilot study on Asian-Indian normative ERG database as part of the international normative ERG database using the ISCEV standard for clinical electroretinography

Vardaan Sood[1], Subhadra Jalali[1], Stuart Coupland[2]
[1]Smt. Kannuri Santhamma Vitreo-Retina Centre,
L. V. Prasad Eye Institute, Hyderabad, India;
[2]University of Oltawa Eye Institute, Canada

Purpose: Pilot study towards establishment of an international normative ERG database for Espion^{TM} users conforming to the ISCEV Standard. *Methods*: Given the greater precision of luminance control of LEDs using pulse-width modulation and the inherent long-term stability of an optoelectronic system, the Espion^{TM} system was used for the study. In a sample of 20 healthy volunteers, the normative values according to the ISCEV standard were established. Normative data values of central tendency (mean or median) and dispersion (standard deviation or 95% confidence limits) were calculated. *Results*: The mean age of the 20 subjects was 25.35 $\pm$ 7.4 years. Mean axial length was 22.94 $\pm$ 0.67 mm; Mean pupil size was 7.97 $\pm$ 0.13 mm. Mean scotopic b-wave amplitudes were 287.9 $\pm$ 82.1 μV with implicit time of 38.15 $\pm$ 3.72 ms. Corresponding median values were 287.9 μV and

37.0 ms. The 5th and 95th percentile values were 177.1 and 432.4 mV for amplitudes and 35.95 and 47.15 ms for the latency. *Conclusions*: This pilot study will pave the way for the collection of similar normative data from a larger number of Asian-Indian eyes that will be incorporated into the Espion clinical protocols to automatically flag those ERG parameters that exceed normal limits, when testing patients.

Poster D3. Effect of inter-flash intervals on the response characteristics of human oscillatory potentials

Yoko Kazato[1], Kazushige Tsunoda[2], Hanazono Gen[3], Mitsuko Yuzawa[4], Manabu Tanifuji[1], Yozo Miyake[5]
[1]RIKEN Brain Sciences Institute, Saitama, Japan; [2]National Institute of Sensory Organs, Tokyo, Japan; [3]Kikkoman General Hospital, Chiba, Japan; [4]Nihon University, Tokyo, Japan; [5]Aichi Syukutoku University, Aichi, Japan

Purpose: The amplitudes of oscillatory potentials (OPs) evoked by the first flash following dark adaptation are known to be smaller than in the subsequent recordings, and only the second or subsequent waveforms are recommended to be retained for analysis. We have recorded human OPs with different inter-flash intervals to reveal the background mechanisms of this phenomenon. *Methods*: ERG responses evoked by white bright flashes (Ganzfeld, 52.4 cd s/m^2) were recorded with a bipolar contact lens electrode in ten normal subjects in the dark condition. Following thirty minutes of dark adaptation, the a- and b-waves (1000–0.5 Hz) and OPs (1000–50 Hz) were measured repeatedly (3–5 times) with the same inter-flash intervals. The inter-flash intervals were set as 5, 15, 30 s, 1, 3 and 5 min. The enhancement of amplitudes by repetition (repetition enhancement) in each recording condition was indicated as the relative amplitudes of the subsequent recordings (SR) to the first recording (FR) in each flash interval (repetition enhancement value = SR/FR). *Results*: The repetition enhancement was prominent in OP2 and OP3: the repetition enhancement values were the maximum when the inter-flash interval was 15 s (2.5 and 1.5 for OP2 and OP3, respectively) and decreased with both shorter and longer intervals. Repetition enhancement was not observed in a-wave, b-wave, OP1 and OP4: the repetition enhancement values for these were the maximum when the inter-flash interval was 5 min (~1.1), and gradually decreased with shorter intervals (0.1–0.8). *Conclusions*: In the dark, the effect of flash repetition on the increase in ERG amplitudes was prominent only in OP2 and OP3, and the maximal effect was obtained with a 15 s interval. The effect of light adaptation or the increase of retinal blood flow by the flash repetition may underlie this phenomenon.

Poster D4. Regional retinal asymmetry of multifocal electroretinogram mfERG responses

Bijoy Nair, Divya Nair, Priya R Reddy, Kiran K Dawani, Parveen Sen
Sankara Nethralaya Medical Research Foundation, Chennai, India

Purpose: To determine whether regional asymmetry of mfERG responses exist in the retinal hemifield and quadrants in normal eyes. *Methods*: MfERGs were recorded in 32 eyes of 23 normal patients (ages 7–65 years) using the VERIS 5.2.1X system. The lens opacity classification (LOCS II N2 P2 C3) was done to exclude patients with significant cataract. The mfERG was done according to ISCEV guidelines. The stimulus array consisted of 103 hexagons (subtending approximately 44 s of arc (″) horizontally and 36″ vertically at the viewing distance of 40 cm) flickering at a rate of 75 Hz according to a pseudorandom m-sequence. The first order kernel response densities were used to calculate the amplitude and implicit times of N1, P1 and N2 in three configurations: the nasal and the temporal field, the superior and the inferior field, and four quadrants. *Results*: The mean nasal N1, P1 and N2 amplitudes were 10.03 ± 1.57 nV/deg^2, 27.63 ± 4.06 nV/deg^2, 12.06 ± 2.1 nV/deg^2, respectively. The temporal N1, P1 and N2 amplitudes were 8.89 ± 1.59 nV/deg^2, 23.93 ± 4.22 nV/deg^2, 10.47 ± 2.05 nV/deg^2, respectively. The difference in the amplitudes was found to be statistically significant for N1 (P = 0.00), P1 (P = 0.00) and N2 (P = 0.00). The P1 latency of the nasal field was 29.24 ± 1.24 ms and that of temporal field was 29.87 ± 1.29 ms. This difference in latency was found to be statistically significant (P = 0.04). There was no significant difference in the amplitudes and implicit times between the superior and inferior fields. There was significant difference in the N1, P1, and N2 amplitudes of the four quadrants (P = 0.018, P = 0.001, P = 0.005, respectively) using Bonferroni multiple comparison test. The implicit times of the quadrants did not show any significant difference. *Conclusion*: Amplitudes of the nasal field were greater than those of the temporal field. The amplitude of both nasal quadrants was greater than the temporal quadrants with largest responses in the superior-nasal quadrant. Significant asymmetry exists between the nasal and temporal fields of mfERG responses. They may be due to shadows cast by the retinal vasculature or cone density. This study shows the regional inhomogeneity that can be expected in a normal human retina.

Poster D5. Electrophysiological findings in children

Li Yu Chen, Audrey Chia
Singapore National Eye Center, Singapore

Purpose: The purpose of this study is to determine the usefulness of electrophysiology tests assessing visual function in children. *Methods*: A retrospective study was done on 159 children aged less than 16 years presenting to the Visual Electrodiagnostic Laboratory at the Singapore National Eye Centre between 2003 and 2006. Data regarding the reason for test and test outcome was collected and analysed. *Results*: The children ranged in age from 3 months to 16 years (mean 8.0 ± 3.9 years). The main reasons for referral were for investigation of poor vision of unknown cause (41%) and assessment of retinal function in the presence of suspected retinal disease (41%). Other reasons included assessment of cortical (5%) or optic nerve function (6%), and suspected functional visual loss (3%). Children were referred from paediatric ophthalmologists (50%), retinal ophthalmologists (27%), general ophthalmologists (12%) and neuro-ophthalmologists (11%). Tests done included full-field ERG in 94%, pattern ERG (38%), flash VEP (23%), pattern VEP (26%) and multifocal ERG (41%). A diagnosis could be made in 90%; these included retinal dystrophy (37%), retinal dysfunction (11%), maculopathy (6%), optic nerve dysfunction (11%) and cortical dysfunction (3%). Normal recordings were obtained in 19%. The tests were inconclusive in 10%, mostly in the 2- to 6-year-old age group, due to borderline recordings (62%) and poor patient co-operation (38%). *Conclusion*: Although electrophysiological testing in children can pose a challenge, for most, useful results could be obtained, providing us with a valuable way assessing visual function.

Poster D6. Assessment of the effect of myopia on the macular function waveforms using multifocal ERG

Vodapalli Harikrishna[1], Swathi Lakshmi[1], Nazimul Hussain[1], Bhanu Rakesh Varma[1], Rishita Nutheti[2], Subhadra Jalali[1]
[1]Smt. Kanuri Santhamma Centre for Vitreo-Retinal Diseases, L. V. Prasad Eye Institute, Hyderabad, India; [2]ICARE, L. V. Prasad Eye Institute, Hyderabad, India

Purpose: To study the effect of different levels of myopia on the macular function waveforms as assessed by multifocal ERG (mfERG) *Methods*: Thirty two eyes of 16 healthy volunteers age 18–35 years (mean 26.5 years) having myopia, underwent mfERG. Data analysis of waveforms was stratified into low myopia in 8 eyes (< –5.00 D sphere), moderate myopia in 8 eyes (> –5.00 to –10.00 D sphere) and high myopia in 16 eyes (> –10.00 to –15.00 D sphere). Amplitudes and implicit times of the 32 recordings were analysed using mean, median and percentiles (5th and 95th) following ISCEV guidelines. An LVP electrode was used for all recordings. *Results*: The central 2° foveal mfERG responses showed mean P1 amplitudes, of 109.5 ± 3.45 μV (SD) in low myopes, 75 ± 6.43 μV in moderate myopes and 42.9 ± 19.9 μV in high myopes. Corresponding peak latencies were 48.25 ± 0.90, 46.0 ± 2.36 and 41.0 ± 16.9 ms. At 15° from fovea, the corresponding P1 amplitudes were 26.2 ± 5.25, 21.25 ± 4.50, and 13.6 ± 6.94 μV and latencies were 43.5 ± 1.45, 43.25 ± 1.48 and 45.4 ± 3.88 ms. *Conclusion*: High myopes have reduced foveal mfERG P1 amplitudes, peak latencies and wider standard deviations as compared to low and moderate myopes. Myopia also affects the amplitudes and latencies in parafoveal locations. Normative databases for mfERG will need stratification based on the level of myopia.

Poster D7. Pilot study on normative data map using multifocal electroretinography in Indian population

Swathi Lakshmi[1], Vodapalli Harikrishna[1], Nazimul Hussain[1], Bhanu Rakesh Varma[1], Rishita Nutheti[2], Subhadra Jalali[1]
[1]Smt. Kanuri Santhamma Centre for Vitreo-Retinal Diseases, L. V. Prasad Eye Institute, Hyderabad, India; [2]ICARE, L. V. Prasad Eye Institute, Hyderabad, India

Purpose: To provide preliminary data of the normative map for multifocal electroretinography (mfERG) in Indian population. *Methods*: MfERGs were recorded from 20 normal subjects with mean age of 35.05 years (range 18–60 years). Subjects with refractive error more than either + 3.00 Dsph or –5.00 D sphere were excluded. The topographical values of responses using the rings and quadrants programs were analysed. Waveform data for four ring groups and for four quadrants data were analysed from the 61 focal responses of the mfERG in each patient. We measured the amplitudes and implicit times among the different rings and quadrants. *Results*: In each subject a negative wave N1, a positive P1 wave and another negative wave N2 was recorded from each eye. In the ring analysis, the mean amplitudes in microvolts of the N1 (–37.15 ± 17.51) P1 (86.56 ± 15.71) and N2 (–74.29 ± 17.01) were largest in foveal area and decreased with eccentricity. In the quadrant analysis the mean N1 (–14.48 ± 3.00) P1 (32.05 ± 6.11) and N2 (–24.58 ± 12.85) were maximum in superior-temporal quadrants of each eye. Using the above pilot study data, sample size for establishing a normative database has been calculated to be 61 eyes for a standard deviation of

±2.00 and precision value of 0.5. This data is being collected in the continuing study. *Conclusion*: The normative data in Indian eyes can be established using the present protocol and this will help in making meaningful comparisons for pathological changes and comparisons with the database from other patient populations.

Poster D8. Comparison of S cones ERG responses obtained with blue and violet LED stimulation

J. R. Charlier, S. Vermandel, J.P. Hugeux
Research & Development department, Metrovision, Pérenchies, France

Purpose: To identify optimal testing conditions for the separation of S-cone responses from rod, M cone and L cone responses on a LED ganzfeld stimulator. *Methods*: ERGs were recorded from three normal subjects with violet (414 nm) and blue (465 nm) ganzfeld flashes presented over a red-orange background (619 nm) with the addition of a lower level (20% in luminance) of green (525 nm) light. *Results*: With blue stimulation, double peak responses were obtained with a first peak around 35 ms and the second peak around 50 ms. When the luminance of the red-orange background was reduced, the amplitude of the first peak increased whereas the amplitude of the second peak remained constant. A clear separation of the second peak was not possible, even with the highest illumination levels (17000 photopic Trolands). With violet stimulation, only one peak around 50 ms was obtained with little amplitude change with the background luminance (from 17000 down to 1000 photopic Trolands). *Conclusions*: These results are in agreement with previous studies using LED stimulation (Arden et al. 1999; Marmor et al. 2004) and showing that a stimulation wavelength below 450 nm is needed for a clear separation of S-cone ERG responses. For this separation, the wavelength used in this study (414 nm) seems as adequate as the wavelengths used in the previous studies (around 440 nm).

Poster D9. Results obtained in our electrophysiological test laboratory in patients with retinal pathology

C. Vilela[1], E. Gonzalez[2], A. Navea[3], J. Romero[3], V.Martin[4], S Soler[1]
[1]Hospital La Fe, Valencia, Spain; [2]Fundaci Ftalmol a del Mediterraneo, Calencia, Spain; [3]Universidad Cardenal Herrera-CEU, Valencia, Spain; [4]Centro De Rehabilitaci Levante, Valencia, Spain

Objectives: Review the results obtained in our laboratory with three electrophysiological tests (or proofs), pattern electroretinogram (PERG), Ganzfeld, full-field electroretinogram (standard ERG), oscillatory potentials (OPs) and the multifocal electroretinogram (mfERG) in patients with glaucoma and with diabetic retinopathy. *Patients and methods*: Following the ISCEV standards we studied 90 patients, 60 with diabetic retinopathy and 30 with glaucoma through PERG, standard ERG and mfERG. We used equipment from Roland Consult Electrophysiological Diagnostic Systems, with a RETIscan V. 4.1.1 software for the ERG and RETIscan v.3.2 software for the mfERG. The patients are in different stages of the illness, arriving at our laboratory in order to establish alterations in the function of the retina. In each of these tests the presence or the absence of valuable alterations is noted. *Results*: From the data obtained in our first study, we observed in the patients that the test that more frequently showed alterations was the OP and to a lesser degree, the mfERG. A large proportion of patients with diabetic retinopathy show alterations in the different tests, showing in almost all alterations in OP and mfERG. There is no defined pattern of alteration shown in the mfERG, however a defined tendency towards the central alteration is shown in patients with diabetic retinopathy. *Conclusion*: From the techniques used in our laboratory, the OP and the mfER seem to be the best indicators of the damage in the retina in this type of patients. Frequently the PERG is also altered but it has not shown pathologic alterations with such frequency.

ORAL SESSION 8: Clinical Electrophysiology: Standards and Variations

Oral paper 39. Review of the ISCEV calibration guidelines

Macolm C. Brown, Anthony C. Fisher, Richard P. Hagan
Royal Liverpool University Hospital, Liverpool, England

The ISCEV calibration Guidelines are being reviewed this year. The guidelines were first published in 1998 and revised in 2003. The current guidelines provide an excellent tutorial in photometry and amplifier characteristics, and go on to propose test protocols for flash and background luminance and pattern luminances and contrast. Since these earlier guidelines were produced there have been technical developments in stimulus generation, which complicate the requirements somewhat, including: (1) Use of light emitting diodes in the generation of flash and light background stimuli. The performance of these differs considerably from the

earlier Xenon flash and tungsten background in both spectral content and, in the case of the flash, the waveform and duration of the stimulus. Measurement of flash and background using standard photometric methods may not fully describe the characteristics of these stimuli, implying equivalence when in fact there are major differences. (2) Pattern stimuli using backlit LCD panels, video projectors, plasma, TFT and other generators for pattern stimuli are now common, and CRT displays are soon likely to disappear from the market. These newer devices all work in different ways and provide stimuli which can be fundamentally different from CRT devices. For instance, most of these devices provide continuous light output during each video frame, so that sequential flashes are changed to a continuous light. The continuous nature of the stimulus has implications for calibration of mfERG systems where the same time integrated stimulus luminance is recorded for a longer dimmer flash as for the short bright stimulus of the CRT.

Oral paper 40. A study of the ISCEV standard normal electro-oculogram with dilated and with natural pupils

J. De Roach[1], D. Candy[1], E. Chelva[1], S. Laurin[1], T. McLaren[1], M. Nosce[2], R. Price[1]
[1]Medical Technology and Physics, Sir Charles Gairdner Hospital, Perth, Australia; [2]Department of Ophthalmology, Sir Charles Gairdner Hospital, Perth, Australia

Purpose: The refinement of the latest (2006) ISCEV standard for the electro-oculogram (EOG), which recommended it be recorded only with dilated pupils has posed a compliance problem for centres with established normal ranges for natural pupils. This preliminary study was designed to examine the relationship between the normal ISCEV standard EOG recorded with natural and with dilated pupils. *Methods*: The EOG was measured in a group of 12 normal volunteers with natural and with dilated pupils according to the 1998 and the 2006 ISCEV standards, respectively. The group comprised 6 females and 6 males ranging in age from 26 to 82 years, with a median age of 35 years. The time lapse between recordings on each individual ranged from 7 days to 7 years, with a median of 4 years. This period was considered acceptable as the EOG has previously been shown to be relatively independent of age. Background light luminance levels of 400 and 100 cd/m^2 were used for the 1998 and 2006 standard protocols, respectively. Dilated pupil diameters ranged from 7 to 9 mm, with a mean of 8 mm, and the average retinal illumination (5024 photopic Trolands) was the same for both procedures. *Results*: There was no significant difference in either the Arden ratio or the dark trough amplitude for the two recording conditions. The light peak latency, on the other hand, was significantly longer ($P < 0.05$) with dilated pupils. *Conclusion*: This study suggests that given the same retinal illumination, there is no significant difference in the primary EOG measure, the Arden ratio, when recorded with dilated or natural pupils.

Oral paper 41. A multi-channel field-specific pattern onset VEP method using interleaved central, peripheral and wide-field peripheral dartboard stimuli: initial clinical experience

Paul F. Weston
Women's & Children's Hospital, Adelaide, Australia

Purpose: To implement a central and wide field-specific pattern onset VEP suitable for children and to investigate possible applications. *Method*: A technique is described for generating field specific pattern onset VEPs so as to allow concurrent acquisition of full and half-field, central (5° radius), peripheral 5° to 30° radius and wide peripheral (30° to 60° radius) responses. The stimulus dimensions are based on the dartboard developed at Aston University in the UK for wide-field pattern reversal. To obtain pattern onset stimulation, two hundred millisecond displays of black and white "dartboard" images interposed with 400 ms periods of 50% grey are presented sequentially using a Neuroscan Stim system on a rear projection screen. Averaging by a Neuroscan Scan computer is triggered prior to the appearance of the respective nine full and half-field dartboard images for the three respective regions. Discreet responses to respective stimuli are obtained for a minimum of five occipital electrodes and a maximum of 30 electrodes positioned in standard EEG montage positions with a linked ear reference. Preliminary studies on a small number of normal teenagers and several patients with visual deficits have been performed. *Results*: Using this method, central, peripheral and wide-peripheral response waveforms may be obtained in single averaging sessions. Sequential half-field and full-field responses extend the information obtained and help confirm the reliability of the results. Responses for normal teenagers are consistent with traditional pattern onset VEPs obtained with checkerboard patterns and show similar morphologies for the respective stimulus eccentricities. Half-field stimulation gives maximal responses in contralateral occipital regions for all stimulus sizes. Responses for three adult patients suggest the technique has applications beyond paediatrics. Field deficits could be corroborated in two patients with

retinal disorders, one of whom was suspected of malingering. In another patient with suspected albinism, the technique was able to provide evidence of optic nerve misrouting affecting central field responses more than those of peripheral fields. *Conclusions*: This approach appears to supplement the established field-specific pattern reversal VEP for children by allowing sequential acquisition of data from segments of the visual field out to very wide angles in single sittings. The use of full and half-field stimuli together, helps verify the reliability of the recordings. The technique appears to offer the potential to obtain useful information, particularly in the peripheral visual fields from patients with limited ability to fixate precisely.

Oral paper 42. Clinical applications of the sweep VEP: a role for principal component analysis?

James Ver Hoeve
Department of Ophthalmology and Visual Sciences, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA

Purpose: To review our clinical experience with the sweep visual evoked potential (sVEP) technique for acuity estimation and to describe a principal component analysis (PCA) method useful for some patients with problematic sVEP records. *Method*: The sVEP stimulus consists of a horizontal sinusoidal luminance-modulated grating that is temporally counter-modulated at 7.5 Hz. The spatial frequency of the grating increases beyond the patient's resolution across 25 fixed steps during the 10 s 'sweep'. An infrared photo-refractor is used to monitor fixation and accommodation. The sine and cosine components of the sVEP data are coherently averaged across sweeps and acuity is estimated as the spatial frequency at the 0-volt crossing of the regression line. This method is compared with principal components extracted from the sVEP-by-trials matrix. *Results*: Paediatric patients are the overwhelming referral (96%) for sVEP testing in our clinic. In an average year, the most frequently referred patient categories are strabismus or amblyopia (29%), developmental delay (24%), and cataract (13%). Recent studies have shown that early sVEP is a better predictor of later optotype acuity than is fixation preference testing in children with strabisumus, amblyopia and Down syndrome. The sVEP can be used to reduce the amount of patching prescribed in infantile cataract patients. The sVEP does less well for predicting later acuity in patients with nystagmus who generally have low signal to noise ratios. Here we show that the typical coherent averaging of the sVEP data may not be optimal in such patients with temporal inconsistencies in the sVEP. A method for extraction of the sVEP based upon principal component analysis shows promise for improved acuity estimation in these patients. *Conclusion*: The sVEP method of acuity estimation provides useful information for the management of most paediatric ophthalmology patients. Principal component analysis may improve sVEP acuity estimation in patients with low signal to noise ratios.

Oral paper 43. Monocular and binocular multifocal electroretinograms; reproducibility, interocular variability and reliability

Marata Janaky, Imre Frejes, Gar Tuboly, Par Kocsis, Gyot Benedek
Department of Ophthalmology/University of Szeged, Szeged, Hungary

Purpose: To evaluate the differences in multifocal ERGs (mfERGs) recorded under monocular and binocular stimulation. *Patients*: Twelve healthy controls with good vision, six patients with strabismic amblyopia with parallel optic axes after successful corrective surgery and six patients with monocular visual loss caused by retinal pathology participated the study. *Methods*: Retiscan equipment provided the stimulation that included 61 hexagons covering the central visual field of 30°. DTL electrodes were used as active electrodes. From the trace array the amplitude values of the central (31st) responses or the average amplitude values of the 7 central first order kernels corresponding approximately to 5° of the visual field were analysed. *Results*: In healthy controls there was no significant difference between the amplitude values recorded under monocular or binocular conditions over the same eyes. A considerable side difference was found, however, between the amplitude values representing the central hexagons (31st kernels). This side difference showed significantly larger variations under binocular conditions than under monocular ones. Average values of the central seven kernels did not show this variability. The highest amplitude values were consistently found within the area of the central seven hexagons. Binocular viewing conditions increased the side differences in patients with monocular visual loss. Amplitude values of the fellow eyes were significantly smaller than those of the amblyopic eyes in strabismic patients, while in patients with organic lesions the non-damaged eye showed higher amplitude values under binocular conditions. *Conclusions*: Our results indicate that monocular and binocular viewing conditions largely influence mfERG results of the central areas. Binocular recordings provide valuable information on side differences of the cone

functions, while variability of the amplitude values is less under monocular conditions. The employment of both recording conditions is recommended in clinical examinations. The use of DTL electrodes enables the extension of recordings in this direction.

Oral paper 44. Optical coherence tomography: a friend or foe for ISCEV? The science (David Keating) and the clinicians' perspective (Pedro Gonzalez)

David Keating, Pedro Gonzalez, Stuart Parks, Sinead M Dudgeon, Angela McCall, Ann McQuiston, Alison Foulis
Gartnavel General Hospital, Glasgow, UK

Purpose: To compare the merits of structural and functional imaging for the clinical diagnosis of retinal disorders. *Methods*: In recent years there have been significant advances in both clinical electrophysiology and in high resolution structural imaging of the retina. In particular, multifocal ERG has added a new dimension to electrophysiology providing both spatial and temporal information on retinal processing. Significant advances have also been made in imaging retinal structure namely Optical Coherence Tomography (OCT). Structural imaging has always complemented functional techniques but the recent advances in high resolution OCT bring a new challenge to our society. Over the past 10 years, we have worked with both structural and functional imaging and recently integrated both techniques in a single instrument (Multimodal Imaging or MMI). We now have an extensive database in which both technologies have been applied in a wide variety of conditions. This presentation is a retrospective look at retinal disorders illustrating the role of both functional and structural techniques and their complementary and sometimes conflicting information. *Results*: New generation OCT machines enable direct high resolution visualisation of retinal structures. In particular, clinical instruments now have axial resolutions of < 3 μm and can resolve the photoreceptor inner-outer segment junction layer. Research systems now incorporate adaptive optics enabling resolution of individual photoreceptors. Specific examples will be shown to illustrate where OCT can provide the key clinical information without the need for electrophysiology. Contrary to this, examples will be shown where electrophysiology detects abnormalities not seen as structural defects and finally examples where electrophysiology shows function to be more extensively affected than the structural abnormality. *Conclusions*: A key role for our society is promoting electrodiagnostic techniques for diagnosis of clinical disorders. We have never used electrophysiology in isolation but as a complementary technique to standard clinical procedures (FFA, fundus imaging, perimetry, etc.). However, the advances in OCT are now so significant that clinicians may be less willing to refer for electrophysiology. Our concerns are that we should embrace this technology or risk a serious impact on our society with the emergence of new imaging societies.

ORAL SESSION 9: Advanced Techniques: The Way Forward

Oral paper 45. Computational methods in focal macular ERG

John Robson
College of Optometry, University of Houston, Texas, USA

Purpose: Characterising recordings of the focal macular electroretinogram (FMERG) in terms of the amplitude and time-to-peak of its a- and b-waves can be troublesome because the low amplitude of the signal results in a low signal-to-noise ratio that makes it difficult to locate the true position of the peaks of the waves. A similar problem exists in determining the position of the peaks and troughs of the pattern electroretinogram (PERG). We aimed to find ways in which FMERG recordings obtained with a 5 Hz square wave stimulus could be smoothed or fitted with an idealised waveform so that the peaks could be simply located as the points of maximum absolute amplitude. *Methods*: We evaluated the ability of two computational procedures for locating the peaks in terms of the variability of the values obtained for repeated recordings: (1) the averaged signals were digitally filtered to remove completely all frequencies above some limit while retaining all lower frequency components unchanged in amplitude and phase; (2) an appropriate mathematical function was fitted to the recorded waveform using a minimum squared error criterion. In both cases the peaks of the a- and b-waves were identified as the points of maximum absolute amplitude in appropriate ranges of time after the light onset. *Results*: Removing all frequency components above 45 Hz or fitting an expression that modelled the summed combination of signals from on- and off-bipolar cells both allowed the peaks of the a- and b-waves of FMERGs to be located automatically at least as reliably as could be achieved by the manual adjustment of cursors. *Conclusion*: In the case of the FMERG it is possible to use computational methods to provide a ''smoothed or idealised waveform'' of

the kind that it is suggested should be envisaged when locating the peaks of the PERG (see ISCEV Standard for Clinical Pattern Electroretinography—2006 update).

Oral paper 46. An expert system for automatic cursoring of the clinical PERG trained on normal and pathological data

Anthony C Fisher[1], Maryke Fox[2], Colin Barber[2], Richard P Hagan[1], Malcolm Brown[1]
[1]Department of Clinical Engineering, Royal Liverpool Univ. Hospital (RLUH), Liverpool, Great Britain, UK; [2]Medical Physics, Queen's Medical Centre (QMC), Nottingham, UK

We have demonstrated recently that the PERG record can be automatically cursored to good accuracy, despite very high levels of noise, using an artificial intelligence approach (SPoC: Smart Positioning of Cursors see www.Liverpooleye.org) In trials, this system outperformed human experts for artificial data and clinically normal PERGs, most dramatically when the human experts returned 'uncursorable' with the poorest SNR (signal-to-noise ratio) records. However, this study highlighted an irresolvable impasse for 'pathological' data. As there are no reference datasets, with unequivocally defined cursor positions, SPoC could not be validated for PERGs that are recorded in clinical practice. In the present study, we reverse the logic. A set of 40 PERG records (nominally 20 normal and 20 pathological) were recorded in Institution 1 (QMC, Nottingham), to ISCEV recommendations using the BioLogic system. These records were reproduced graphically in Institution 2 (RLUH, Liverpool) as plots on axes with undeclared units. These records were then cursored (three cardinal points) by human experts (three in Nottingham and six in Liverpool) and results collated.

An expert system similar to the original SPoC was constructed using a combination of three independent artificial neural networks based on multi-layer perceptrons using the 40 PERG records as input data and the median values of the human expert cursor times and peak latencies as target outputs. Each PERG record was represented in the training dataset as 250 examples randomly perturbated in time and amplitude with random uniform noise. Amplitudes for each cursor were determined, post hoc of the timings as estimated by the artificial neural network, by fitting local 5th order polynomials with frequency responses appropriate to each cardinal cursor point as inferred from the ISCEV Standard PERG waveform. This presentation will examine the performance of the human experts and that of the trained Expert System for the training data itself and for a series of artificially constructed PERG models with unambiguous (explicitly-known) cursor positions based on perturbations of the ISCEV Standard. A real-time demonstration of the construction of the training dataset, the training procedure and operation of the Expert System on previously unseen PERG records will made using an Internet connection to the Liverpool MatLab server using a MatSOAP implementation (www.matsoap.org.uk). All software is written in MatLab and JavaScript, and is freely-available to the ISCEV community as open source code.

Oral paper 47. Optimising steady state sweep VEPs to stimuli like the central FDT target: comparison to psychophysical thresholds in early glaucoma detection

Vaegan, Mark A. Elia, Jacqueline Zheng
Optometry and Vision Science, University of New South Wales, Sydney, Australia

Purpose: To maximize signal noise ratios (SNRs) of steady-state (ss), swept-contrast visual evoked potentials (VEPs) to stimuli like the central frequency doubling technology (FDT) target. To compare how VEP and corresponding subjective thresholds detect early glaucoma. *Methods*: We found which electrode type, electrode position, pattern luminance profile, spatial frequency, field size, temporal frequency, modulation mode and data combination methods gave the best SNR. Both eyes of 5–10 young normals were used for each parametric study. Vertical 0.25 cycles/degree sine or square bars or checkerboards of various sizes in various field areas with $34 \times 20°$, were reversed sinusoidally in time at 7.5, 12.5, 18.5 or 37.5 reversals/s or appeared/disappeared at the same rates in Hz. Monocular sweep ssVEPs (15 sweeps, 64-1% contrast, octave steps, 4×1 s traces) were averaged from four almost orthogonal channels (Fpz, Oz, MTR, MTL (inion-1 cm) reference). SNR was the ratio of the magnitude of the discrete Fourier transform at the signal frequency to the mean magnitude of the two adjacent frequencies. T2 circ and a Pythagorean sum channel were also calculated. For the clinical comparison both eyes of 58 subjects, blindly classified by an independent clinician as normal (49), ocular hypertension (8) or as suspected (21), mild (7) or moderate (30) primary open angle glaucoma, were tested with 18 reversals/s VEPs and with psychophysics. A full FDT test was done on 25 subjects. VEP thresholds were estimated by exponential fits to the rising phase of the amplitude by contrast curve and subjective thresholds to the same stimuli by QUEST in a 2AFC task. *Results*: Gold cup electrodes were more tractable and had a non-significant

advantage at high contrasts. Noise was similar across contrasts and across channels, increased in the sum channel and decreased exponentially with frequency. Reversal, 18 reversal/s, and the sum channel all significantly increased SNR ($P < 0.05$). Response magnitude was largest for checks and smaller for bars, then for sine patterns, respectively. All spatial frequencies < 2 cycles/degree and areas >10° were similar. VEP contrast functions were flat to contrast above 2% then exponential, except at 2 cycles/degree where a parvocellular pattern appeared. In individuals, even small deviations from the exponential perturbed the threshold severely. The full FDT had similar error rates to those previously reported. There were no clinical differences in VEP or psychophysical contrast thresholds. *Conclusions*: Optimal VEP parameters and threshold measurement methods are now better defined. They do not suggest a My generator. The Pythagorean sum of orthogonal channels gives higher SNR and avoids source selection with repeated measures by condensing all data to one representation of the underlying dipole. Sweep ssVEPs can be used to compare parameters over groups but not to reliably classify patients, unlike adaptive methods that put all tests near threshold.

Oral paper 48. Objective Evaluation of the Focal Rod ERG

Tom H. Margrain, Alison M. Binns
School of Optometry and Vision Sciences,
Cardiff University, Cardiff, UK

Purpose: To objectify evaluation of the focal rod ERG waveform, where the signal to noise ratio is low, a model based on the underlying physiology was used to extract clinically relevant variables. *Methods*: Data from single cell recordings of human rod photoreceptors and ERG derived rod bipolar cell responses were obtained from the literature (Kraft et al. 1993; Cameron et al. 2006) and fitted with model based on the probability density function of the gamma distribution. Having established the model variables that best describe each of the main subcomponents of the rod ERG, the equations describing rod photoreceptor and biopolar cell components were summed, together with a third, 'inner retinal', component to form a model capable of summarizing the entire rod ERG data that had previously been obtained in the clinic (Binns and Margrain 2006) and clinically relevant parameters were extracted objectively. *Results*: (1) The three component model provided a good description of the focal rod ERG, when the signal to noise ratio was high, and the characteristics of each subcomponent were physiologically plausible. (2) When applied to data where the signal to noise ratio was low it was possible to extract objective information about the amplitude and implicit time of the a-wave and b-wave even when their location was unclear subjectively. *Conclusion*: By using models based on retinal physiology it is possible to make best use of all the data in clinical ERG recordings. The application of such models not only facilitates objective quantification of established parameters such as 'a-wave implicit time' but also, information about the characteristics of the underlying sub-components, which may ultimately have more clinical relevance.

Oral paper 49. The frequency response of the short wavelength cones (S-cones) and its application to clinical cases

Chris Hogg, Magella Neveu, Amy March
Moorfields Eye Hospital, London, UK

Purpose: To determine the ERG frequency responses of the short wavelength cones and investigate the possibility of using the frequency characteristics to enhance isolation of the response. *Methods*: S-cone ERGs were recorded at a range of luminance levels and frequencies, under both light and dark adapted conditions, and also using two stimulus wavelengths. *Results*: Using standardized clinical luminance values produced a frequency response curve in excess of that normally associated with rods and, depending on the cursored points, a tuned responses curve for the S-cone specific component. *Conclusion*: The stimulus frequency can be used to enhance the isolation of the S-cone response from that of any light adapted rod contribution.

Oral paper 50. To optimise the decimation of binary sequences for use in multifocal recording

Malcolm Brown, Anthony Fisher, Richard Hagan
Royal Liverpool University Hospital, England, UK

Purpose: To optimise the decimation of binary sequences for use in multifocal recording. *Methods*: We have created a mathematical tool, which will examine a binary sequence and check its properties. With a given set of restrictions entered by the user, such as the number of separate channels required, the number of base periods in the recording epoch, which (how many) higher-order Kernels to test for, etc., the tool finds a set or sets of sequences from the master sequence which have the least number of possible overlaps or contaminations between channels. *Results*: Examples from long and short sequences will be illustrated.

Conclusions: Using this online tool, binary sequences can be tested for suitability in multifocal recording. Not surprisingly, short sequences provide only a limited number of options when a large number of channels are required, and are therefore most in need of examination and optimisation. This tool will be demonstrated live using a web-based implementation over the Internet via a MatSOAP connection (www.matsoap.org.uk). All software (MatLab and JavaScript) will be available as Open Source code from www.Liverpooleye.org.

Oral paper 51. Evaluation of retinal dysfunction using multifocal electroretinography in patients with an established clinical and electrophysiological diagnosis of AZOOR

Vasumathy Vedanthum[1,2], Maria M. Neveu[2], Anthony G. Robson[2,3], Alan C. Bird[2,3], A. R. Webster[2,3], Graham E. Holder[2,3]
[1]Aravind Eye Hospitals, Madurai, India;
[2]Moorfields Eye Hospital, London, UK;
[3]Institute of Ophthalmology, London, UK

Background: Acute zonal occult outer retinopathy (AZOOR) is a poorly defined condition characterised by photopsia and visual field loss in the presence of relatively mild or even absent fundus changes. Although sporadic case reports concerning multifocal electroretinographic (mfERG) abnormalities in AZOOR have appeared in the literature, a substantial case series has yet to appear. This report addresses the mfERG findings in 13 patients with a clinical diagnosis of AZOOR. *Design*: Retrospective observational case series. *Methods*: The medical notes of 13 patients with an established clinical diagnosis of AZOOR who had undergone mfERG were reviewed. *Results*: MfERG demonstrated central and/or paracentral areas of macular dysfunction that could not be predicted from the fundus appearance. Areas of mfERG abnormality corresponded with the visual field abnormalities in five patients. Sparing of the central mfERG response was associated with preserved visual acuity; reduced central responses were associated with central scotomas and decreased vision. *Conclusions*: MfERGs may demonstrate the spatial extent and severity of macular dysfunction in AZOOR, that may not be obvious clinically. MfERGs are a valuable addition to diagnostic electrophysiology and in the objective assessment of this condition.

Oral paper 52. Seasonal change in cone and rod ERGs in patients with seasonal affective disorder treated with light therapy

M. Hebert[1], M.-P. Lavoie[1], G. Bouchard[2], A. Sasseville[1], M.-C. Charron[1], A.-M. Gagne[1], P. Tremblay[1]
[1]Dept of Ophthalmology, Laval University; [2]Dept of Psychiatry, St-Sacrement Hospital, Quebec, PQ, Canada

Purpose: Our goal was to investigate for the first time the impact of seasons (autumn versus summer) and light therapy on cone and rod ERG functions in patients affected with seasonal affective disorder (SAD). *Methods*: Twenty-two patients with SAD symptoms were sex and age matched as far as possible with 16 normal controls. In SAD patients, cone and rod ERG luminance-response functions were obtained in autumn before and after 2 and 4 weeks of daily light therapy (30 min at 5,000 lux SADelite lamp, Northern Light Technologies) as well as in summer when natural remission occurs. Normal controls were evaluated once in autumn and once in summer. *Results*: Cone V_{max} b-wave amplitudes were on average 17% lower in SAD patients when compared to controls ($P = 0.01$). Rod retinal sensitivity (log K value) was 0.13 log units lower in SAD patients ($P = 0.01$). After 4 weeks of light therapy (but not after 2), both cone (Vmax) and rod (log K) parameters were not significantly different than the controls ($P > 0.05$). In summer, both parameters were not significantly different between patients and controls ($P > 0.05$) and normal controls did not demonstrate any seasonal change in retina function ($P > 0.05$). *Conclusions*: This is the first objective evidence of cone and rod function anomalies in SAD patients occurring during the depressive episode only. This represents also the first report of a biological effect of light therapy on retinal function. Although the origin of the seasonal change in retina function in SAD patient is still unclear, we believe that a neurotransmitter imbalance (such as serotonin) could explain both the presence of the symptoms observed in these patients and the ERG findings.

ORAL SESSION 10: Scope of Electrophysiological Evaluation in Retinal Vascular Diseases

Oral paper 53. The experimental model of retinal ischemia in rabbits

Marina V. Zueva, Irina Tsapenko, Vladimir E. Tankovsky, Andrey N. Ivanov, Nadezhda E. Shvetsova, Olga V. Mizerova
Moscow Helmholtz Research Institute of Eye Diseases, Moscow, Russian Federation

Purpose: To create a reproducible retinal ischemia (RI) model basing on the clinical and electrophysiological data. *Methods*: The experimental rabbit's model of an acute RI was reproduced by laser photocoagulation (LC) of I-III orders retinal vessels for dosed effect, at external fundus quadrants (power intensities: 500–1000 mV at 0.1–0.5 s exposures, 200–500 μm spot diameter). The volume of affected vessels stretched along a zone of one optic nerve head diameter; the number of coagulates depended on the achievement of an expected effect—vascular obscuration. The full-field 1 Hz-ERG and 30 Hz-flicker ERGs (1.7 cd s/m^2) were recorded before the RI modelling, 1 h after and 1, 7, 14 and 22 days after this with the handheld ERG system 'Mjolner' (Ephios AB, Sweden). *Results*: The narrow-directed, trans-pupilary LC of retinal vessels (and corresponding paravascular retina) resulted in an after-burn inflammatory reaction, and the reaction of surroundings tissue followed by the occlusion and retinal ischemia. Ophthalmoscopic examinations showed the vessels obscuration and desolation. Two to 3 weeks after the LC, we observed the irregular calibre of vessels again and a pale retinal tissue within the visibly differentiated zone of the LC. An increase in the a-wave amplitude (up to 130%) 10–15 min after the LC was shown, which was followed by its reduction by 20–40% on days 1 through 22. The b-wave amplitude decreased by 20–30% in spacious retinal ischemia, and increased by 10–20% when the mildly affected zone was created. The mean b/a ratio sharply decreased just after the LC and increased then to supernormal values, reflecting the photoreceptor involvement in the retina response to ischemia. The flicker ERG amplitude slightly decreased immediately after the LC and remained reduced up to the end of follow up. *Conclusion*: The method offered provides a stable, simply reproducible model of non-traumatic, dosing experimental RI. The specific alterations of retinal function can be objectively controlled by ERG dynamics.

Oral paper 54. Effects of different doses of taurine on oxygen-induced retinopathy in developing rats

Luz Marina Rojas[1], Maury Palma[2], Yaurinis Rodriguez[1], Menfis Romero[1], Pierre Lachapelle[3], Lucimey Lima[2]
[1]IIBCA-Universidad de Oriente, Venezuela;
[2]IVIC, CaracasSan Antonio de los Altos, Venezuela;
[3]Department of Ophthalmology, McGill University/ Montreal Children's Hospital, Canada

Purpose: One of the effects of oxygen-induced retinopathy (OIR), is that the retina suffers severe functional and structural damages. Taurine is an essential amino acid to retinal maturation with known free radical scavenging properties. The purpose of this study was to determine the dose of taurine required in order to avoid the damages caused by hyperoxia and to evaluate oxidative stress in different periods of hyperoxia. *Methods*: Four groups (of 10 newborn rats and their mothers) were exposed to hyperoxia (80 ± 1% O2) during 14 days. Each mother drank water with 0%, 2%, 3% and 4% taurine. Scotopic electroretinograms (ERGs) were obtained 30 days after birth, following which the rats were sacrificed and the retina prepared for histology. For the analysis of oxidative stress, two groups of rats were exposed to hyperoxia from birth and 6, 9, 12 and 14 days after birth, but only one mother drank water with taurine at 3%. For every period the levels of MDA and SOD were analyzed in the retina, following Bioxytech LPO-586 and Bioxytech SOD-525, respectively. *Results*: Compared to the scotopic ERG amplitudes of their untreated littermates (178 μV), the scotopic ERGs of taurine 2%, 3% and 4%-treated rats demonstrated a significant amplitude increase of 52% (367 μV), 56% (400 μV) and 43% (312 μV), respectively. For both, treated and untreated rats, a disminution of the MDA levels (32% and 33% respectively) was observed for the period of exposure to hyperoxia during 0–14 days compared with that of 0–6 days. The SOD levels increased between the periods of 0–6 and 0–14 days. Animals treated with taurine showed a 33% increase and untreated rats an increase of 50%. *Conclusion*: The dose of 3% taurine gave the best protection of the rod function. MDA levels indicate that the highest oxidative stress occurs in hyperoxia periods of 0–6. SOD increases with the hyperoxia period.

Oral paper 55. The role of electroretinographic responses in assessing the progress of diabetic retinopathy

Young-Hoon Ohn, Su-Eun Park, Tae-Kwann Park, Jin-Kyun Oh
Soonchunhyang University Hospital, Bucheon, Korea

Purpose: To investigate the clinical significance of electroretinographic (ERG) responses in assessing the progression of diabetic retinopathy. *Methods*: ERGs were recorded on 28 normal controls and 134 diabetic patients. Of those, 97 patients had diabetic retinopathy with different stages. ERGs were recorded according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standard. Amplitudes and implicit times of the ERG responses including photopic negative responses (PhNRs) were compared at different stages of diabetic retinopathy. *Results*: Amplitudes of oscillatory potentials were significantly reduced in the mild non-proliferative diabetic retinopathy (NPDR) stage ($P < 0.001$). Amplitudes of cone b waves, 30-Hz flicker responses and PhNRs were reduced significantly in the moderate NPDR stage ($P < 0.001$). The Receiver operating characteristic curves showed that the amplitudes of the ERG responses were more sensitive and specific than implicit times in diabetic retinopathy patients. *Conclusions*: These results suggest that oscillatory potentials are good indicator of changes in retinal function in early stage of diabetic retinopathy and, cone b wave, 30-Hz flicker and PhNR are good indicators in advanced stage.

Oral paper 56. The photopic negative response of flash electroretinography in non-proliferative diabetic retinopathy

Dezheng Wu, Hongling Chen
Zhongsan Ophthalmic Center, Visual physiology, Sun Yat-sen University, Guangzhou, China

Purpose: To study how the PhNR of flash ERG is affected in human non-proliferative diabetic retinopathy (NPDR). *Methods*: PhNR was elicited with red stimuli (1, 5 and 7 cd s/m^2 with 4 ms duration) and blue background (10 cd/m^2). Standard Ganzfeld flash ERG was produced according to the ISCEV standard for the clinical electroretinography (2004). Eighty-one diabetic patients with NPDR at different stages were examined. Forty-three age-matched normal controls were also studied. *Results*: The amplitude of PhNRs progressively decreased with the progression of NPDR, while the implicit time prolonged. The amplitudes of PhNRs in control group (71.1 ± 16.7, 78.1 ± 15.1 and 83.0 ± 17.9 μV with stimuli of 1, 5 and 7 cd s/m2, respectively) were larger than those of diabetic patients with NPDR at different stages, including patient with no apparent retinopathy (0 stage) (61.6 ± 17.1, 69.0 ± 17.8 and 71.0 ± 16.8 μV). The amplitude of PhNRs in patients with stage II retinopathy (38.1 ± 8.0, 45.9 ± 9.0 and 44.6 ± 9.6 μV) was smaller than that of patients with stage 0 and stage I (56.0 ± 12.8, 64.5 ± 13.2 and 65.4 ± 13.4 μV). The amplitude of PhNRs in patients with stage III retinopathy (28.6 ± 9.8, 33.7 ± 10.8 and 35.2 ± 12.1 μV) was smaller than that of patients with stages 0, I and II. The implicit time of PhNRs in control group (69, 71 and 73 ms) was shorter than that of patients with stage II (73, 76 and 78 ms) and III (81, 83 and 84 ms). The implicit time of PhNRs in patients with stage III retinopathy was longer than that of patients with stage 0 (69, 72 and 75 ms), stage I (70, 74 and 74 ms) and stage II. All the differences above were statistically significant, while the amplitudes of standard ERGs including OPs in patients with no apparent retinopathy and in those with stage I were not different from those of controls. However, the amplitudes of OPs, rod b-waves, combined a-waves, 30 Hz responses, cone a-waves and of cone b-waves in patients with stages II and III declined significantly compared with those of the controls. Except for the OPs, the extent of the effect on standard ERG amplitudes was far less than for the PhNRs. Compared to controls, amplitude of OPs in patients with stage II decreased by 37.1%, while PhNRs decreased by 46.4%, 41.3% and 44.5% with stimuli of 1, 5 and 7 cd s/m^2, respectively. However, amplitude of OPs in patients with stage III decreased by 59.5% and similarly PhNRs decreased 60.0%, 56.9% and 56.2% with stimuli of 1, 5 and 7 cd s/m2, respectively. *Conclusions*: The amplitudes and implicit times of PhNR can indicate the inner retinal function in patients with non-proliferative diabetic retinopathy. PhNRs are more sensitive than standard ERGs in evaluating the function of inner retina. There is a potential role for PhNR in assessing inner retinal damage and evaluating the effect of treatment.

Oral paper 57. Visual function evaluation in retinopathy of prematurity

Rulong Gao, Dezheng Wu, Tianqin Guan
Zhongsan Ophthalmic Center, Zhongsan Hospital, Sun Yat-sen University, Guangzhou, China

Purpose: To investigate the visual function in retinopathy of prematurity (ROP). *Methods*: All subjects were divided into three groups: group 1: 25 cases (50

eyes) of full-term infants, group 2: 25 cases (50 eyes) of healthy preterm infants, group 3: 37 cases (50 eyes) of ROP patients (gestational age was less than 32 weeks and birth weight was low). The ages at testing in most of the patients from group 3 were 2- to 9-month-old, and only one was 4-year-old. The objective visual function was tested by convention electroretinography (ERG) examination. The amplitudes and implicit times of a- and b-waves of each response were measured to evaluate the retinal function of the patients. *Results*: (1) The waveform of each response could be recorded from both the full-term infants and healthy preterm infants. The b-wave amplitudes of the scotopic combined (rod and cone) responses of 4-month-old full-term infants and preterm infants were 395.14 μV and 337.80 μV, which was 65.42% and 55.92%, respectively of the normal adult scotopic combined (rod and cone) b-wave amplitude (604.0 μV). (2) Comparing implicit times between group 1 and group 2, the b-wave of the rod ERG and a- and b-waves of the scotopic combined (rod and cone) response were delayed significantly in group 2 ($P < 0.01$). The a- and b-wave amplitudes of the scotopic combined (rod and cone) response and b-wave amplitude of the cone ERG were decreased significantly in group 2 ($P < 0.01$). (3) In group 3, ERGs were non-recordable in 47.3% of the patients. The responses in 27.1% of the patients were decreased markedly, and in 24.3% of patients slightly or moderately. Only 1.3% of the patients (the 4-year-old patient) had normal responses. *Conclusions*: (1) The retina develops and matures continually even after birth. (2) The retinal development in preterm infants is slower than that of full-term infants. (3) ROP could occur in early after birth and needs to be followed up early. (4) ERG examination can provide an effective method in evaluating the retinal function in ROP.

Oral paper 58. Electrophysiologic and anatomical studies after intravitreal injection of bevacizumab (Avastin) for macular oedema due to retinal vein occlusions

Rohit Shetty, A. Sivakami, Ajoy Vincent
Narayana Nethralaya, Banguluru, India

Purpose: To evaluate the short-term electrophysiologic responses and anatomical effects of intravitreal injection of bevacizumab for macular oedema due to vein occlusions. *Methods*: Ten eyes of 10 patients with macular oedema due to vein occlusions underwent complete ophthalmic examination including Snellen visual acuity testing, full field electroretinography (ff ERG), multifocal electroretinography (mfERG), optical coherence tomography (OCT) scanning and intraocular pressure (IOP) measurement, at baseline, 1 week and 1 month after intravitreal bevacizumab. *Results*: Ff ERG did not show any change in waveforms from baseline following intravitreal injection of bevacizumab. Average mfERG macular responses within central 10° showed mild to moderate increase in P1 amplitude ($P < 0.05$) at 1 month after treatment as compared to the baseline recordings in all subjects. No changes were seen in the implicit time. Central retinal thickness at baseline, a week and 1 month after intravitreal injection of bevacizumab was 592.65, 422.88 and 366.53 μm respectively ($P = 001$). There was no correlation between visual acuity, central retinal thickness changes and mfERG responses following treatment. IOP remained within normal limits. *Conclusions*: Intravitreal injection bevacizumab resulted in reduction in the central retinal thickness and mild to moderate improvement in the mfERG amplitudes. Although retinal vein occlusion is predominantly an inner retinal layer disease, macular oedema sets in when there is a breach to the inner and outer blood retinal barriers. Hence mild to moderate increase in P1 amplitude in mfERG in the central 10° following bevacizumab injection suggests that the drug probably has no toxic effects on the outer retinal layers. Therefore the off-label drug probably has no toxic effects in the short-term. However, randomized controlled, long-term electrophysiological studies in adequate number of patients are required to establish the safety of the drug.

THE 2007 EMIKO ADACHI AWARD LECTURE

Restoring neuroretinal function: new potentials

Eberhart Zrenner
Department of Ophthalmology, Institute
for Ophthalmic Research, University of Tübingen,
Germany

Several concepts of how to restore vision in blind or visually impaired persons have been developed based on implanting electronic devices into the eye or around the optic nerve or into the visual cortex in order to evoke useful visual sensations. Since 1995, our consortium has worked on sub-retinal silicon ''chips'' and has meanwhile developed a so-called ''active'' retinal microphotodiode array (MPDA), based on in vitro measurements and using various animal models (Schwahn et al. 2001). This lecture will present the multitude of steps that have been necessary to apply this technique in a clinical study of seven patients showing the feasibility of this approach and thereby opening the

door to new therapeutic possibilities for patients, blind from outer retina diseases.

In vitro experimentswith chicken and RCS rat retinae using a sandwich technique, in which recordings are made by means of multi-electrode arrays either from the inner or the outer retina (Zrenner et al. 1999; Stett et al. 2000) have revealed that:

(1) Charge injections of about 1 nC per electrode are sufficient to excite post-receptoral retinal neurons.
(2) Electrode distances of 50–150 μm in the outer retina can be resolved in ganglion cell recordings.
(3) Retinae with completely degenerated photoreceptors (RCS rats, 160 days and older) can still be excited by sub-retinal electrodes in a proper, spatially-organized manner.
(4) Surface coating of MPDAs (e.g. with laminins) can improve cell adhesion and biocompatibility (Guenther et al. 1999).

In vivo experiments have revealed that:

(1) Inner retinal layers are well preserved in the central retina, as shown by comparative histological studies of human and animal forms of degenerative retinal disorders (see Zrenner et al. 1997).
(2) Two surgical approaches for safe introduction of the devices have been developed: (a) ab interno via the classical trans-vitreal access to the retina, and (b) ab externo via a scleral flap near the limbus through the sub-retinal space (like in a tunnel) to the back of the eye (Sachs et al. 2005; ARVO 1999; Shinoda et al., ARVO 2004).
(3) Inner retinal layers are well preserved after long-term implantation of subretinal MPDAs in pigs (up to 28 months).
(4) MPDAs remain fixated at stable subretinal positions as investigated in both rabbit and pigs.
(5) MPDAs initially showed some damage of the silicon oxide surface of the implant. A suited coating had to be developed.
(6) Spatially sensitive electrically evoked cortical potentials recorded with multi-electrode and optical recording from the visual cortex of rabbit and pig following acute electrical sub-retinal stimulation via electrode foil strips reveal a spatial resolution of at least 1° (Eckhorn et al. 2006).

From these findings the characteristics of an active sub-retinal implant were determined that is suited for *implantation in the human eye*. A clinical study has been completed, where the wire-bound MPDA is implanted for 4 weeks into one eye of seven blind retinitis pigmentosa patients. The active implant consists of approximately 1500 light-sensitive cells on a surface of 3×3 mm (each cell containing an amplifier and an electrode of 50×50 μm, spaced at 70 μm) as well as a 4×4 array of identical electrodes, spaced at 280 μm, for direct stimulation (DS), chronically implanted next to the foveal rim in 6 patients. MPDA (“chip”) and DS array are positioned on a small subretinal polyimid foil powered via a sub-retinal, trans-choroidal, retro-auricular, trans-dermal line. Within a 0.1 mm layer, each of the 1500 cells has circuits that adapt the strength of the electrical signal to the nerve cell to the strength of the brightness of the object to be seen and its surroundings. So far, no other chip has been presented with a similar high resolution that is ready for implantation and this is the first active sub-retinal chip ever implanted in patients (see Zrenner ARVO 2006; ARVO 2007).

Stimulation parameters for each DS electrode and chip, activity and sensitivity can be controlled independently by a comfortable software that allows transformation of the orientation of visual space to the orientation of the electrode field and allows setting of individual stimulation parameters in the stimulation box via a wireless transmitter. Moreover, all stimulation parameters and patients’ “yes” or “no” responses to each parameter are recorded automatically by a particular software (Sailer, ARVO 2005).

For patient selection, corneal DTL-electrodes and an alternative forced choice method was used to determine electrical excitability of the retina and of optic nerve transmission in normals and patients with degenerative retinal disease; this determination of phosphene threshold with corneal electrodes has turned out to provide an important criterion for the suitability of patients for electrical retinal prostheses (Gekeler et al. 2006).

A safe trans-choroidal sub-retinal access is mandatory for a successful chronic implantation of a cable bound visual prosthesis. In order to establish the prerequisites for human implantation, results of long-term implantations in adequate animal models were performed. Domestic pigs had received sub-retinal cable bound stimulation devices for 6 month (Sachs et al. 2005; ARVO 2006). The same *trans-choroidal procedure was applied in the 7* patients without adverse events such as retinal detachment, bleeding, infection etc. (Sachs et al., ARVO 2007); radio-diathermy and a specially designed implantation instrument were used to penetrate the choroid without bleeding; silicone oil was used as a tamponade; there were no problems with transdermal cables. OCT examinations turned out to be very valuable assessing the sub-retinal alignment of the device and the stability of its position in relation to the retina. OCT scans demonstrated small intra-retinal densifications that corresponded in fundoscopy to well demarcated changes at the edges of the chip (Kuttenkeuler et al., ARVO 2006). After explanation,

which took place according to the 4-week study plan, the retina showed only minor changes at the implantation site. Fluorescence angiography (FA) in all patients showed that the capillary bed was nicely visible over the implant region due to blockade of background fluorescence. In 5 patients some drop-out of the retinal capillaries was observed. Some degree of retinal microaneurysm formation and various degrees of vessel rarefactions in the region overlying the MPDA and DS were seen (Gekeler et al., ARVO 2007). One patient decided to keep the implant for a period of more than 1 year. FA findings remained stable, only microaneurysm formation increased in the last 3 months. One eye developed mild macular oedema. The retina of one patient after >30 years of blindness did not respond to electrical stimulation within the safety limit. Four subjects had pattern recognition via direct electrical stimulation and two patients reported visual perceptions through the MPDA. The changes of retinal vascularization during the observation period were not correlated to functional outcome and even eyes with marked findings reacted to electrical pattern stimulation.

A battery of computerized, standardized tests for patients with visual prostheses was developed to quantify *the functional outcome* (Zrenner et al., ARVO 2004). Visual perception of brightness elicited by applying biphasic voltage impulses from 1 to 2,5 V (t = 3 ms) was assessed using a scale from 5 (very strong) to 0 (none); additionally double impulses with differences up to 0.8 V between two stimuli (10 s interval) were applied. Electrical stimulation of rows, columns and blocks of four electrodes allowed some patients to clearly distinguish horizontal from vertical lines and positions, respectively. Under optimal conditions, dot alignment and direction of dot movement was properly recognized, if three neighbouring electrodes were switched on simultaneously or sequentially at 1 s intervals (Zrenner et al., ARVO 2007). Brightness perception of spots varied from scale 0 to 5 in a linear manner if voltages between 1.5 and 2.5 were applied (randomly six times) to a square of four electrodes. This corresponds to a charge increase of approximately 0.23 mC/cm^2 for each of the five steps. A difference in brightness between two consecutive pulses was discerned, if a difference in charge of at least 16 μC/cm^2 was applied. If equal charges were applied to both conditions, the second flash always was perceived as slightly dimmer irrespective of the stimulation level. Subjective brightness amplification phenomena were observed at medium stimulation levels and at certain frequencies. The subjective size of spot perception upon stimulation of a square of four electrodes increased from 1 to 5 mm at arms length, if the voltage was increased from 1.5 to 2.5 V. In SLO micro-perimetry of the chip, single light spots down to 100 to 400 μm in diameter were detected, allowing the patient to localize a white plate on a black tablecloth correctly (Zrenner et al., ARVO 2007). Apparently sub-retinal electrical multi-electrode stimulation can, in principle, provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters. A small b-wave-like electrically evoked retinal potential was recorded with amplitudes up to 10 mV and peak latencies near 40 ms after stimulation with short signals (0.5–4 ms) of 2.5 V.

The brief symptom inventory (BSI) by Derogatis, a validated 53-item questionnaire, was used for the assessment of variations in *psychological stress* of the patients before and during the 4-week study. The sum score total Global Severity Index (tGSI) was used for evaluation (Peters et al., ARVO 2007). In the first six blind patients participating in the pilot trial, the BSI showed that study participation was tolerated well. At screening all subjects (mean 50.33 ± 12.17) were in the normal range of the tGSI. The difference at close out visit compared to screening (t-test: mean diff 6.17 ± 8.95; P = 0.08) showed a tendency to lower values in a sense of better emotional balance at the end of trial participation.

In summary: Sub-retinal, electrical, multi-electrode stimulation can provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters and does produce a new kind of electrical retinal potentials. However, it is still not clear what type of image a patient will be able to see after prolonged use of such devices. It is expected, that, as in cochlear implants for hearing, the brain can learn to interpret images from their features, like learning to interpret art sketches in normal vision. Nevertheless, the clinical study has shown the potential of this approach to help blind patients in object localization; active, power-driven, sub-retinal, electronic, multi-photodiode arrays thereby can improve mobility and visual communication.

References (other than the ARVO abstracts quoted in the text)

Eckhorn R, Wilms M, Schanze T, Eger M, Hesse L, Eysel UT, Kisvarday ZF, Zrenner E, Gekeler F, Schwahn H, Shinoda K, Sachs H, Walter P (2006) Visual resolution with retinal implants estimated from recordings in cat visual cortex. Vision Res 46:2675–2690

Gekeler F, Messias A, Ottinger M, Bartz-Schmidt KU, Zrenner E (2006) Phosphenes electrically evoked with DTL electrodes: a study in patients with retinitis pig-

mentosa, glaucoma, and homonymous visual field loss and normal subjects. IOVS 47:4966–4974

Guenther E, Troeger B, Schlosshauer B, Zrenner E (1999) Vision Research 39:3988–3994; Sachs H, Schanze T, Wilms M, Rentzos A, Brunner U, Gekeler F, Hesse L (2005) Subretinal implantation and testing of polyimide film electrodes in cats. Graefe's Arch Clin Exp Ophthalmol

Schwahn HN, Gekeler F, Kohler K, Kobuch K, Sachs H, Schulmeyer F, Jakob W, Gabel VP, Zrenner E (2001) Studies on the feasibility of a subretinal visual prosthesis: data from Yukatan micropig and rabbit.

Graefe's Arch Clin Exp Ophthalmol 239:961–967
Stett A, Barth W, Weiss S, Haemmerle H, Zrenner E (2000) Vision Res 40:1785–1795

Zrenner E, Miliczek K-D, Gabel VP, Graf HG, Günther E, Haemmerle H, Höfflinger B, Kohler K, Nisch W, Schubert M, Stett A, Weiss S (1997) Ophthalmic Res 29(5):269–280

Zrenner E, Stett A, Weiss S, Aramant RB, Guenther E, Kohler K, Miliczek K-D, Seiler MJ, Haemmerle H (1999) Vision Res 39:2555–2567

Zrenner E (2002) Will retinal implants restore vision? Science 295:1022–1025

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